Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN

PSICOLOGIA

Ciclo XXXII

Settore Concorsuale: 11/E1

Settore Scientifico Disciplinare: M-PSI/02

POST-LESIONAL FUNCTIONALITY OF THE VISUAL SYSTEM IN HEMIANOPIC PATIENTS

Presentata da: Mattia Pietrelli

Coordinatore Dottorato **Supervisore**

Prof.ssa Monica Rubini **Prof.ssa Caterina Bertini**

Esame finale anno 2020

Table of contents

Abstract

Hemianopic patients suffer for a loss of conscious vision in part of the visual field. The present work aimed to investigate the functionality of the visual system after lesions to visual cortices, by studying the spontaneous electrophysiological activity and the residual visual processing. The first three studies revealed the presence of alterations in the spontaneous alpha oscillatory activity during resting-state. Specifically, hemianopic patients showed a slowdown of the speed of alpha oscillations and a reduction of the amplitude of alpha activity in the lesioned hemisphere, resulting in an interhemispheric imbalance of the activity in the alpha range. Moreover, hemianopics showed also a reduction of alpha functional connectivity in the posterior regions of the lesioned hemisphere. However, the residual activity in the alpha range seemed functionally reactive, since hemianopics showed the typical alpha desynchronization in the transition from the eyes-closed to the eyes-open resting-state. More importantly, the spontaneous alpha activity predicted the visuospatial performance, suggesting that the resting-state activity in the alpha range, might be a biomarker for the functionality of the visual system. Notably, oscillatory patterns were more severely impaired in hemianopics with right lesions, suggesting a central role of the right posterior cortices in coordinating the spontaneous oscillatory activity. In the last study, unseen distractors presented in the blind visual field were able to interfere with the execution of saccades toward seen targets presented in the intact field, suggesting the presence of an implicit visual processing for stimuli presented in the blind visual field. However, only left-lesioned hemianopic patients showed implicit processing for the unseen distractors, suggesting that the right hemisphere might also contribute to this interference effect. Overall, the post-lesional oscillatory patterns and the implicit visual processing in the absence of awareness seem to reflect an impaired but residual functionality of the visual system in hemianopic patients.

Chapter 1

1.1. The organization of the visual system

1.1.1. The retina

The retina converts light in electrochemical signal due to the presence of two types of photoreceptors: the cones and the rods. In optimal lighting conditions, vision is mainly mediated by cones, whereas rods are more effective for night vision, i.e. the scotopic vision, due to their greater sensitivity to light. Moreover, cones show optimal response to different wavelengths of light, i.e. different colors, specifically, there are cones tuned to short (blue), middle (green) and long (red) wavelengths. Cones and rods are not equally distributed across the retina, in particular between the fovea and the periphery (Osterberg, 1935). The macula is located temporal to the optic nerve (diameter 5.5 mm), within the macula there is the fovea (diameter 1.5 mm), and within the fovea, the foveola (diameter 0.35 mm). There are about 15 times more cones in the fovea than in the peripheral part of the retina, providing an excellent visual acuity (Hirsch and Curcio, 1989). On the contrary, rods are quite absent in the fovea. With increasing eccentricity, there are fewer cones and more rods, and therefore less visual acuity. From the photoreceptors, electrochemical signals go through bipolar cells to the ganglion cells. In the fovea, each bipolar cell receives input from a single photoreceptor, whereas in the peripheral part of the retina a bipolar cell receives the inputs from multiple photoreceptor cells, further supporting the higher spatial resolution of the fovea compared to the peripheral part of the retina.

There are three types of ganglion cell: 80% percent of ganglion cells are P cells, 10% are M cells, and 10% are K cells. The different types of ganglion cells organize in segregated visual pathway, i.e. the parvocellular, the magnocellular and the koniocellular pathways (Polyak, 1941; Kaplan and Shapley, 1986; Hendry and Yoshioka, 1994). This peculiar computational organization start from the ganglion cells of the retina and it is maintained through the entire visual system. P cells are highly concentrated in the fovea, indeed they show extremely small receptive field with specialization for high spatial acuity, color vision and fine stereopsis (Livingstone and Hubel, 1988). On the contrary, M cells are more concentrated in the peripheral part of the retina, indeed they show larger receptive field with specialization for low spatial resolution (Croner and Kaplan, 1995), motion detection, coarse stereopsis, but

blind to color differences (Livingstone and Hubel, 1988). Relatively little is known about K cells, because it has been difficult to study in isolation. However, K cells seem to be involved in color vision (Hendry and Yoshioka, 1994). The last type of ganglion cells is involved in the control of circadian rhythms, due to their sensitivity to changing in overall luminance level (Hattar, Liao, Takao, Berson, and Yau, 2002). The two optic nerves start from the optic disk of each eye's retina and go to the optic chiasm. In the central part of the optic disk, i.e. the optic cup, there are no photoreceptors, which gives rise to the monocular blind spot (Mariotte, Pecquet, and Justel, 1668). Each optic nerve conveys information from the nasal and temporal part of the retina. Specifically, each nasal hemiretina receives visual information from the peripheral ipsilateral visual hemifield, whereas each temporal hemiretina receives information from the central contralateral part of the visual field. The optic chiasm is the structure where the axons from the two optic nerves decussate. Specifically, axons from nasal ganglion cells cross and join axons from temporal ganglion cells from the contralateral eye. In this way, each following optic tract will propagate information from only the contralateral hemifield, specifically the visual information from the ipsilateral temporal hemiretina and the contralateral nasal hemiretina. The two optic tracts deliver visual information from the optic chiasm to different subcortical nuclei.

1.1.2. The subcortical nuclei

The majority of axons from the two optic tracts targets the ipsilateral Lateral Geniculate Nuclei (LGN). The retinotopic organization is still preserved in the LGN (Kupfer, 1962). The LGN is divided in six layers, preserving the anatomical and functional segregation between the P, M and K pathways and between axons from the temporal and nasal hemiretinas (Chacko, 1948; Leventhal, Rodieck, and Dreher, 1981).

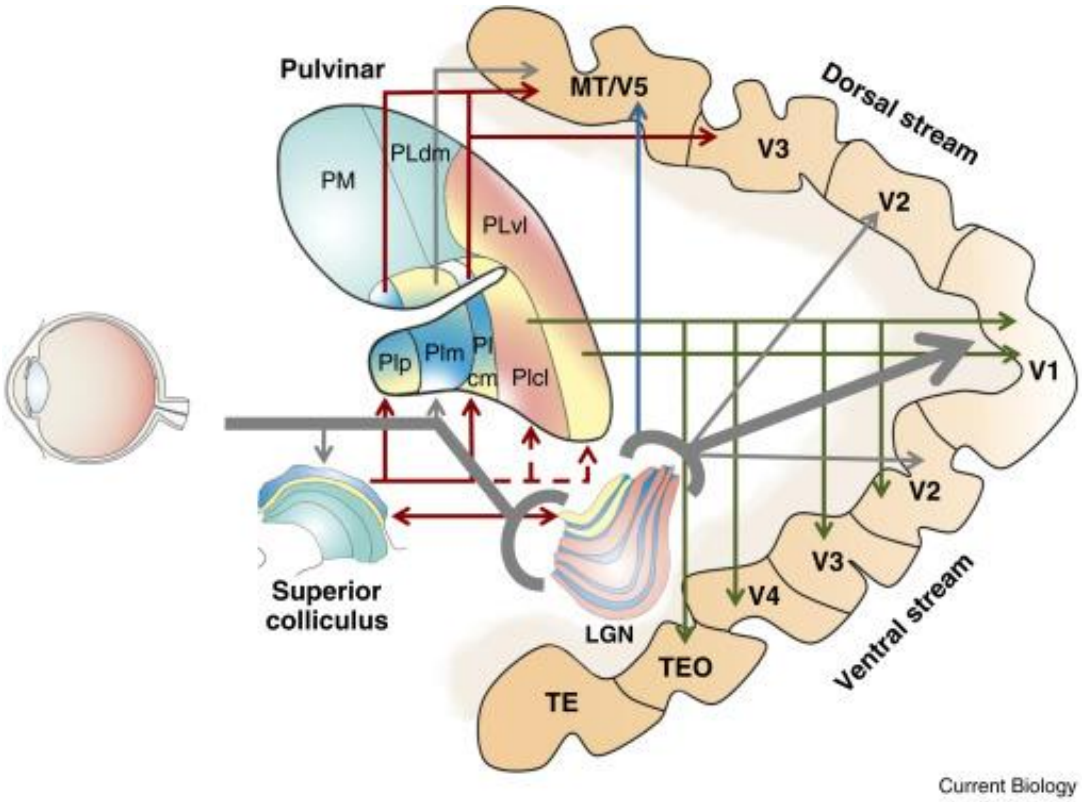

Figure 1. Connections from the eye to the visual cortex involving intermediate relays in LGN, Superior Colliculus and Pulvinar (taken from Tamietto and Morrone, 2016).

The LGN is commonly seen as a relay station for the visual information travelling to and from the cerebral cortex. Indeed, the axons arriving from the retina are only the 5-10% of the total afferents to the LGN (Van Horn, Erişir, and Sherman, 2000). Specifically, the majority of afferent inputs to the LGN comes from the sixth layer of the visual cortex. Consequently, LGN has a pivotal role in the modulation and filtering of incoming visual information from the retina (Prasad and Galetta, 2011). From the LGN, visual information is sent to the primary visual cortex (V1) through the two optic radiations. Each optic radiation is divided in a temporal branch that convey visual information from the contralateral superior part of the visual field, and a parietal branch that convey the contralateral inferior part of the visual field (Van Buren and Baldwin, 1958).

Part of the axons from the two optic tracts targets the ipsilateral thalamic Pulvinar nuclei. Like the LGN, Pulvinar nuclei receive massive modulation from the visual cortex, specifically from the fifth and sixth layer (Chalupa, 1991). The Pulvinar nuclei have widespread connections between very different subcortical and cortical areas, providing it a main role in

the modulation of brain activity based on requirements of spatial attention (Petersen, Robinson, and Morris, 1987; Rafal and Posner, 1987).

Another part of the axons from the two optic tracts targets the ipsilateral Superior Colliculi (SC). The SCs are mainly involved in the programming and generation of orienting behaviors, specifically eyes and head movements toward salient stimuli. The SCs are anatomically and functionally divided in superficial and deep layers. The superficial layers of each SC are sensitive only to visual information, representing the contralateral visual field in a visuotopic criteria (Cynader and Berman, 1972). To the other side, the deep layers of each SC integrate sensory information from different modalities with a motor map to generate eyes and head orienting movements toward unexpected stimuli. Moreover, the representation of the foveal part of the visual field is magnified in the SC like in all the other part of the visual system. Both superficial and deep layers exchange information with several thalamic nuclei, first the Pulvinar, and also with the extra-striate visual cortices bypassing the LGN (Sommer and Wurtz, 2004a; 2004b).

A small portion of the axons from the two optic tracts targets the Pretectal nuclei. The Pretectal nuclei are involved in the regulation of pupillary size. Moreover, the small portion of the axons from the two optic tracts that conveys information about the level of general luminance targets the Suprachiasmatic nucleus (Hattar et al., 2002). The Suprachiasmatic nucleus monitors the environmental luminance level in order to discriminate between day and night. The connection between the Suprachiasmatic nucleus to the Pineal gland provides the neural basis for the control of the circadian rhythms through melatonin release.

1.1.3. The primary visual cortex

The temporal branch of the optic radiations arrives in the inferior part of the primary visual cortex, whereas the parietal branch makes synapse with the superior part of the primary visual cortex. In this way, the visual field is fully represented on the primary visual cortex in an inverted way, both to the respect of the horizontal and vertical axes. All the axons that run inside the optic radiations are connected to the fourth layer of the primary visual cortex (Gennari, 1782). P and M pathways conserve their anatomical segregation also in the input to the fourth layer of the primary visual cortex, targeting respectively the 4Cb and the 4Ca sublayers (Hubel and Wiesel, 1962). Primary visual cortex neurons are organized in

dominance columns sensitive to specific orientations of luminance contrast, representing the basic step for the contours detection (Hubel and Wiesel, 1962). In addition, initial processing of color, brightness, and direction of motion is supported by the primary visual cortex neurons (Tootell, Hamilton, Silverman, and Switkes, 1988). The primary visual cortex then sends visual information to extra-striate cortices along the dorsal and ventral pathways of the brain cortex.

1.1.4. The higher-order cortical visual regions

The different extra-striate visual areas are organized into two anatomically and functionally segregated cortical streams. While the ventral stream seems to mediates visual recognition of objects, also called the "what" pathway, the dorsal stream is specialized for the processing of spatial relationships and manipulation of objects, also called the "where" or "how" pathway (Mishkin, Ungerleider, and Macko, 1983; Goodale, Milner, Jakobson, and Carey, 1991). Indeed, a lesion to the inferior temporal cortex, the higher-order region of the ventral stream, impairs severely the performance of macaques in visual discrimination tasks, specifically in objects recognition and in the discrimination on different colors, visual patterns or shapes. On the contrary, performance in visuospatial tasks, such as visually guided reaching and discrimination between different relative distances between objects, was not affected at all. To the other side, a lesion to the posterior parietal cortex, the higher-order region of the dorsal stream, produces the opposite behavioral pattern: a severe impairment in the performance to the same visuospatial tasks, whereas the performance to the visual discrimination tasks is not affected at all (Mishkin et al., 1983).

The ventral stream begins in the P pathway layer 4Cb of the primary visual cortex. Then, the ventral stream continues to V2, V4 and finally to the inferotemporal cortex (Shipp and Zeki, 1985; Sincich and Horton, 2002; Zeki, 1980). In parallel, the dorsal stream begins in the M pathway layer 4Ca of the primary visual cortex and continues to V2 and V3 (Shipp and Zeki, 1985; Sincich and Horton, 2002). From V2 and V3 the dorsal stream reach the motion-specialized extra-striate areas V5/MT, and finally the posterior parietal cortex (Boussaoud, Ungerleider and Desimone, 1990; Tootell, Reppas, Kwong, Malach, Born, Brady, Rosen, and Belliveau, 1995). The processing in the dorsal stream is faster compared in the ventral stream, indeed axons in the dorsal stream contain more myelin than in the ventral stream

(Schmolesky, Wang, Hanes, Thompson, Leutgeb, Schall, and Leventhal, 1998; Nowak and Bullier, 1997). The mechanisms of attention interact with processing of visual information at all stages (Desimone and Duncan, 1995; Treue and Maunsell, 1996; Reynolds, Pasternak, and Desimone, 2000).

1.2. The visual system after a brain lesion

1.2.1. The hemianopia syndrome

Hemianopia involves the loss of conscious vision in a part of the visual field due to the lesion of the primary visual pathway. Specifically, any lesion along the pathway from the retina through the LGN to the primary visual cortex can lead to hemianopia. The loss of conscious vision in hemianopia affects all the daily living activities and may result in injuries due to falls or difficulties to avoid obstacles. Therefore, identifying and treat the hemianopia symptomatologic profile can have a significant positive effect on the quality of life of patients.

Different etiologies can lead to hemianopia syndrome. In adults, the most common cause of hemianopia is the stroke, indeed hemianopia is found in 8-10% of stroke patients and in the 52-70% of hemianopic patients the cause of hemianopia is a stroke (Zhang, Kedar, Lynn, Newman, and Biousse, 2006; O'Neill, Connell, O'Connor, Brady, Reid, and Logan, 2011). Moreover, the 14% of hemianopia cases are due to a traumatic brain injury whereas the 11% are due to a tumor (Zhang et al., 2006). On the contrary, the most common causes of hemianopia in children are tumor (27%–39%), brain injury (19%–34%), infarction (11%–23%), and cerebral hemorrhage (7%–11%) (Kedar, Zhang, Lynn, Newman, and Biousse, 2006; Liu and Galetta, 1997).

The location of the brain lesion along the primary visual pathway directly produces different types of hemianopia. Specifically, a lesion to the optic tract produces a contralesional hemianopia, with the loss of conscious vision in the contralesional visual field. Moreover, a lesion to the temporal branch of the optic radiation produces a superior contralesional quadrantopia, with the loss of conscious vision in the upper contralesional quadrant of the visual field. On contrary, a lesion to the parietal branch of the optic radiation produces an inferior contralesional quadrantopia, with the loss of conscious vision in the lower contralesional quadrant of the visual field. Finally, lesions to the primary visual cortex produce different clinical outcomes. Since the entire visual field is represented in the primary

visual cortex, a lesion will affect the part of the visual filed corresponding to the lesioned site. However, the large macular neural representation in the occipital lobe often prevents the loss of the central 2-10° of the visual field after an occipital brain lesion. Indeed, the visual field is not equally represented through the occipital lobe, where the 10-30° of the central vision is represented by the 50-60% of the entire occipital lobe (Korogi, Takahashi, Hirai, Ikushima, Kitajima, Sugahara, Shigematsu, Okajima, and Mukuno, 1997; McFadzean, Brosnahan, Hadley, and Mutlukan, 1994). The sparing of macular field areas can also occur after a lesion of the optic tracts or the optic radiations (Zhang et al., 2006). Retro-chiasmatic lesions never impair visual acuity, whereas retinal conditions affect it severely.

1.2.2. The hemianopia syndrome beyond the loss of conscious vision

The loss of conscious vision in a part of the visual field seems not to be the only consequence of a retro-chiasmatic lesion, since also the higher-order visuospatial representation is affected as well.

Most of the hemianopic patients shows impairment in the oculomotor scanning behavior in both the blind and the healthy visual fields, although the impairment is especially pronounced in the blind visual field (Zihl, 1995a; Ishiai, Furukawa, and Tsukagoshi, 1987; Chedru, Leblanc, and Lhermitte, 1973). In other words, a lesion of the primary visual pathway affects the visual scanning behavior in the entire visual field. Specifically, hemianopic patients show an abnormally high rates of repetition of scan paths and fixations, as well as hypometric saccades toward the blind field, that leads to a significantly longer search times compared to healthy participants (Zihl, 1995a; Passamonti, Bertini, and Làdavas, 2009; Ishiai et al., 1987; Zangemeister and Oechsner, 1996; Tant, Cornelissen, Kooijman, and Brouwer, 2002b). It can be hypothesis that hemianopic patients fail in comparing what is present in the current spatial location with what was present in the region inspected before. As a consequence, the ability to integrate different portions of the visual field into a higher-order global representation of space can be impaired, and visual exploration and continuous visual information processing are disturbed (Zihl, 1995a).

The impairment in visuospatial abilities in hemianopia is showed also in line bisection tasks. When hemianopic patients are asked to cut in half a horizontal line, they usually show a bias toward the blind field. Several possible explanations have been proposed, even if the topic is

still debated. In the first hypothesis, bisection errors are consequences of the visual field loss (Nielsen, Intriligator, and Barton, 1999). However, bisection errors are still found when hemianopic patients are tested with lines little enough to be seen entirely without the need of eye-movements. A second explanation claims that the bisection errors arise from a long-term strategic adaptation to the visual field loss (Barton, Behrmann, and Black, 1998; Doricchi, Onida, and Guariglia, 2002). Specifically, several authors suggest that the increase in fixations towards their blind field can represent a compensatory mechanism that patients learn to overcome the visual field loss. However, bisection errors are present also in simulated hemianopia (Schuett, Dauner, and Zihl, 2011; Mitra, Abegg, Viswanathan, and Barton, 2010) and acute true hemianopia (Machner, Sprenger, Hansen, Heide, and Helmchen, 2009), therefore weakening the idea of a long-term compensatory and strategic adaptation explanation. In another hypothesis, authors suggest that an additional damage to the extra-striate regions adjacent to the optic radiations or striate cortex can explain the visuospatial impairment (Zihl, Sämann, Schenk, Schuett, and Dauner, 2009). However, similar bisection errors are present also in simulated hemianopia (Schuett et al., 2011; Mitra et al., 2010), where participants without any brain lesion were tested.

In a similar way, the impaired visuospatial performance in hemianopia are evident also in the Greyscales task (Mattingley, Bradshaw, Bradshaw, et al., 1994; Mattingley, Bradshaw, Nettleton, et al., 1994). The task requires participants to judge which of two identical left–right mirror-reversed brightness gradients appears darker overall. Since the two stimuli are identical, any tendency to respond more to a side compared to another represents a visuospatial bias toward that visual hemifield. In particular, hemianopic patients show an anomalous and consistent tendency to judge darker the greyscale with the dark part in the intact visual field (Mattingley et al., 1994a; Mattingley, et al., 1994b; Mattingley, Berberovic, Corben, Slavin, Nicholls, and Bradshaw, 2004; Tant et al., 2002b; Tant, Brouwer, Cornelissen, and Kooijman, 2002a).

Even if the causes are still debated, hemianopic patients show an impairment in visuospatial abilities and the allocation of spatial attention concurrently with the main loss of conscious vision in a part of the visual field. It is reasonable to think that the impairment in these higher-order spatial representations further worsen the patients' clinical condition, leading to both a perceptual and attentional shrinking of the visual field.

1.2.3. The impact of hemianopia in the everyday life

The visual field defect, combined with visuospatial impairments, strongly affects several activities of the daily living, indeed patients often report difficulties avoiding obstacles, reading, driving and engaging in recreational activities, such as watching television (Goodwin, 2014; de Haan, Heutink, Melis-Dankers, Brouwer, and Tucha, 2015).

Even if patients with hemianopia do not meet the legal driving requirements, some hemianopic patients continue to drive illegally (Alberti, Peli, and Bowers, 2014; Bowers, Tant, and Peli, 2012). Moreover, hemianopic drivers show impaired detection and reactivity to pedestrians on the side of their visual field defect (Alberti et al., 2014; Bowers, Ananyev, Mandel, Goldstein, and Peli, 2014; 2009). In particular, hemianopic patients make more but smaller head scans toward the blind visual field compared to healthy participants in a driving simulation. These aberrant scanning behavior leads hemianopic patients to detect virtual pedestrian less than half of the time compared to healthy participants (Bowers et al., 2014). Moreover, hemianopic patients show difficulties in controlling the vehicle position, in modulating the speed to the traffic condition and in reacting to unexpected events, when evaluated on real driving scenarios (Elgin, McGwin, Wood, Vaphiades, Braswell, DeCarlo, Kline, and Owsley, 2010).

Hemianopic patients also show impairment in the reading ability, probably due to the reduced visual field and the aberrant eye scanning patterns. In particular, while left hemianopia can involve only difficulties in finding the subsequent line of text (Zihl, 1995b), right hemianopic patients show severe difficulties, because for an efficient reading 7-11 letters ahead in the right visual field are usually needed (Kerkhoff, 2000). Indeed, these patients are not able to find efficiently words in the blind visual field with eye-movements. Specifically, hemianopic patients show disorganized eye movement patterns, prolonged fixation time, reduced saccadic amplitude, and an increased number of regressive saccades (Zihl, 1995b). However, hemianopic patients with sparing of the macula part of the visual field tend to have less impairment in reading (Zihl and von Cramon, 1985; Papageorgiou, Hardiess, Schaeffel, Wiethoelter, Karnath, Mallot, Schoenfisch, and Schiefer, 2007).

Hemianopic patients also show difficulties in the navigation in the everyday environment, resulting in disorientation, trouble crossing the street in traffic, bumping into objects, inability

to detect hazards, and increased risk of falling (Goodwin, 2014). Indeed, hemianopic patients show much longer search times during visual search tasks, because of the disorganized greater number of saccades toward the blind field (Zihl, 1995a).

1.2.4. Residual visual abilities in hemianopia: blindsight patients

Despite the absolute loss of conscious vision in a part of the visual field, in rare cases hemianopic patients are still able to detect, localize, and discriminate visual stimuli presented in the blind visual field above the chance level, a syndrome called "blindsight" (Pöppel, Held, and Frost, 1973; Weiskrantz, Warrington, Sanders, and Marshall, 1974). In order to verify the presence of such unexpected behavior, two different kind of approach are used, specifically direct and indirect approaches. In direct approaches, participants are asked to guess about the presence/absence or between different features of stimuli presented in their blind visual field, by choosing between a limited number of options. The procedure to ask a participant to discriminate the feature of visual stimuli presented in their blind field between a limited set of alternative responses is commonly called alternative forced choice (AFC) procedure. In indirect approaches, participants are asked to respond to stimuli presented in the intact visual field while task-unrelated stimuli are presented in the blind visual field. Therefore, if the performance for stimuli presented in the intact visual field is modulated by the presentation of stimuli in the blind field, then unseen stimuli presented in the blind field must have been unconsciously processed.

By using the AFC procedures for stimuli presented in the blind field, some hemianopic patients showed to be able to localize, by manual, verbal or eyes-movement response, the position of a stimulus presented briefly at different eccentricities in the blind field (Pöppel et al., 1973; Weiskrantz et al., 1974; Perenin and Jeannerod, 1975; Blythe, Kennard, and Ruddock, 1987). These patients showed also to be able to discriminate between the presence or absence of both stationary and moving stimuli when presented in the blind field (Stoerig, 1987; Stoerig et al., 1985; Stoerig and Pöppel, 1986; Stoerig and Cowey, 1989; 1991; Magnussen and Mathiesen, 1989). Moreover, blindsight patients are able also to discriminate between two different stimulus orientations (Weiskrantz, 1990; Morland, Ogilvie, Ruddock, and Wright, 1996), stimulus displacements (Blythe et al., 1987; Blythe, Bromley, Kennard, and Ruddock, 1986), motion directions and different colors (Stoerig, 1987; Stoerig and

Cowey, 1991; Brent, Kennard, and Ruddock, 1994). Also, reliable shape discrimination was found in few hemianopic patients, demonstrated by how the reaching and grasping dynamics were appropriate with the particular shape presented (Perenin and Rossetti, 1996). Also, indirect approaches show residual blindsight abilities in some hemianopic patients. Faster reaction times were found for responding to stimuli presented in the intact visual field when an unseen stimulus was delivered concurrently in the blind visual field compared to when no unseen stimulus was delivered. In order to provide the behavioral enhancement, the unseen stimulus has to be presented within 100-200 ms before or after the presentation of the target stimulus in the intact visual field, in line with congruency effect usually found in healthy participants (Marzi, Tassinari, Aglioti, and Lutzemberger, 1986; Corbetta, Marzi, Tassinari, and Aglioti, 1990). However, not all kind of visual stimuli presented in the blind visual field are able to improve the behavioral performance for stimuli presented in the intact field. Whereas the presentation of a simple grey stimulus in the blind visual field improved both reaction times and pupillary responses for stimuli concurrently presented in the intact field, the presentation of a purple stimulus in the blind field failed to produce the same enhancements. Furthermore, the behavioral and physiological improvements for the unseen grey stimulus were paired with a selective activation in the SC that was not present when the purple stimulus was delivered. Since the SC is blind to purple color because of the absence of afferent fibers from retinal S-cones, a direct involvement of the SC in the visuomotor integration of grey stimuli presented between the two hemifields was suggested (Tamietto, Cauda, Corazzini, Savazzi, Marzi, Goebel, Weiskrantz, and de Gelder, 2010). In addition, also color information from the blind visual field can influence the color perception in the intact field. Specifically, the color of an afterimage perceived from the intact visual field of a blindsight patient was modulated by the surrounding color presented in the blind visual field (Pöppel, 1986). In another study, the perception of the direction of illusory motion was modulated by unseen stimuli presented in the blind visual field (Stoerig and Fahle, 1995). However, the influence of stimuli presented in the blind visual field can reveal also a higher level of unconscious processing. Specifically, unseen words presented in the blind visual field are able to bias the semantic interpretation of words presented in the intact visual field (Marcel, 1998), demonstrating that visual information delivered in the blind visual field can be sometime fully processed by blindsight patients. Overall, inside the blindsight phenomena

there are very different visual residual abilities that could broadly range from simple luminance detection to semantic processing.

In addition to the above mentioned visual residual abilities, visual processing of emotional stimuli in the absence of awareness has received special attention in investigations on blindsight patients. For instance, one of the most studied blindsight patients, GY, shows performances above the chance level in different type of AFC tasks, when asked to guess about the emotional content of faces presented in his blind visual field. Specifically, GY was able to discriminate above chance level both in 2AFC and in 4AFC tasks, between happy, sad, angry and fearful faces (De Gelder, Vroomen, Pourtois, and Weiskrantz, 1999). However, it has been proposed that emotional faces present very peculiar features that can be learnt without the need to understand their emotional content. Therefore, GY might had simply discriminated between different patterns of visual stimuli, confirming his blindsight ability to discriminate above chance level between different shapes (Cowey, 2004). However, the same affective blindsight performance is showed by a patient with a bilateral lesion to the primary visual cortex, therefore suggesting that these patients are really processing emotion-related information instead of simply discriminating between previously seen complex facial images (Hamm, Weike, Schupp, Treig, Dressel, and Kessler, 2003; Pegna, Khateb, Lazeyras, and Seghier, 2005). The affective blindsight discrimination abilities are not confined to facial expressions but occur also in the processing of emotional bodies. Specifically, patients GY and TN were able to discriminate above the chance level in a 2AFC task between angry and neutral emotion delivered by body postures (Van den Stock, Tamietto, Sorger, Pichon, Grézes, and de Gelder, 2011; Van den Stock, Tamietto, Zhan, Heinecke, Hervais-Adelman, Legrand, Pegna, and de Gelder, 2014). Similarly to the classical blindsight, the affective blindsight was investigated with indirect methods. Patients GY showed faster reaction time to responding for facial emotional expressions presented in the intact visual field when a congruent stimulus was presented concurrently in his blind visual field. Specifically, when a pair of congruent sad, fearful or angry faces were concurrently delivered in both the intact and the blind hemifields. The facilitatory effect on responses to emotional faces was evident both when two congruent emotional faces were presented simultaneously in both hemifields, and when two congruent right and left half of emotional faces were presented divided between the hemifields (de Gelder, Pourtois, van Raamsdonk, Vroomen, and Weiskrantz, 2001).

These unconscious visual abilities seem to be mediated by the activity of alternative visual pathways, which are usually spared after postchiasmatic lesions. Indeed, different pathways might subserve the wide range of blindsight abilities that could range from the simple motion detection to the discrimination of emotional facial expression. The SC seems to have a central role in determining blindsight responses driven by visually guided eye movements (Spering and Carrasco, 2015). Indeed, the SC is usually spared from lesions inducing hemianopia and it is involved in the programming and generation of saccadic eye-movements in healthy participants (Krauzlis, Lovejoy, and Zénon, 2013). Moreover, the SC seems also involved in the discrimination of motion stimuli presented in the blind field, because of its connections with several subcortical and cortical brain structures relevant for motion processing. Specifically, primate studies suggest the presence of connections between the SC and the V5/MT, a cortical areas specialized in the processing of motion stimuli (Sommer and Wurtz, 2004a; 2004b). Indeed, primate V5/MT neurons still show burst of activity selective for different motion directions after the removal of V1 (Rodman, Gross, and Albright, 1989; 1990; Girard, Salin, and Bullier, 1992; Azzopardi, Fallah, Gross, and Rodman, 2003). In addition, a direct pathway between LGN and MT (Ajina, Kennard, Rees, and Bridge, 2014), fibers connecting the Pulvinar and MT (Bourne and Morrone, 2017) projecting from the SC to MT passing through the Pulvinar (Tran, MacLean, Hadid, Lazzouni, Nguyen, Tremblay, Dehaes, and Lepore, 2019) has been also proposed to have a role in blindsight for motion processing. Moreover, the emotional processing in the absence of awareness seen in affective blindsight patients has been attributed to the sparing of the subcortical pathway that projects visual information from the SC to the Amygdala, via the inferior Pulvinar (Tamietto, Pullens, de Gelder, Weiskrantz, and Goebel, 2012; Rafal, Koller, Bultitude, Mullins, Ward, Mitchell, and Bell, 2015).

1.2.5. Residual visual abilities in hemianopia: patients without blindsight

Recently, a series of studies showed the presence of implicit visual processing also in hemianopic patients that do not show the expected performance in direct tasks, i.e. in hemianopic patients with performance at chance level in 2AFC tasks. A recent study, with hemianopic patients without the expected blindsight performance to AFC tasks, showed an alpha desynchronization selectively for motion stimuli compared to static stimuli when presented in the blind visual field (Grasso, Pietrelli, Zanon, Làdavas, and Bertini, 2018). Since

alpha desynchronization is commonly found reflecting visual cortex activation (Pfurtscheller, 2001; Romei, Brodbeck, Michel, Amedi, Pascual-Leone, and Thut, 2008a) and visual processing (Pfurtscheller, Neuper, and Mohl, 1994), this electrophysiological activity seems to represent the presence of an implicit visual processing in the absence of awareness for motion stimuli in hemianopic patients without blindsight. The peculiar selectivity for motion stimuli in implicit visual processing suggests the involvement of a spared subcortical visual pathway particularly sensitive to motion. Indeed, authors suggested the involvement of the alternative pathway that links retinal input to the motion sensitive extra-striate MT areas through the SC, as the main candidate to sustain the implicit visual processing of motion stimuli in hemianopic patients without blindsight (Grasso et al., 2018).

In a series of different studies, hemianopic patients without affective blindsight, i.e. who perform at the chance level in discriminating between different emotional facial expressions when presented in their blind field, demonstrated the presence of an implicit visual processing specific for fearful facial expressions presented in their blind visual field (Bertini, Cecere, and Làdavas, 2013; 2017; Bertini, Pietrelli, Braghittoni, and Làdavas, 2018; Cecere, Bertini, Maier, and Làdavas, 2014). Specifically, hemianopic patients without blindsight showed a reduction of response time to discriminate emotional faces presented in their intact visual field when fearful faces were concurrently presented in their blind visual field. In contrast, no response facilitation was found when the concurrent face presented in their blind visual field was happy or emotionally neutral (Bertini et al., 2013). In a subsequent ERP study, the presentation of fearful faces in the blind visual field was able to increase the N170 amplitude evoked by emotional faces presented in the healthy visual field (Cecere et al., 2014). Since N170 is a well-known ERP correlate of facial structure processing, results suggest that the presentation of fearful faces can facilitate the visual analysis of facial expression presented in the healthy visual field. Furthermore, the response facilitation from the presentation of fearful faces in the blind field can generalize also outside the facial domain, extending the same facilitation to the discrimination of simple Gabor patches presented in the healthy visual field (Bertini et al., 2017). This fear-specific implicit visual processing that induces a facilitation in the behavioral and electrophysiological responses to stimuli presented in the intact field (Bertini et al., 2013; Cecere et al., 2014; Bertini et al., 2017) suggests the presence of a mechanism able to prioritize the visual processing of the external environment, and has been

attributed to the activity of the subcortical circuit encompassing the SC, the Pulvinar and the Amygdala, spared after V1 damage (Tamietto et al., 2012; Rafal et al., 2015). In line with this hypothesis, the response facilitation found in these studies was absent in hemianopic patients with a lesion of the Pulvinar, suggesting that the Pulvinar plays a pivotal role in convey fear-related visual information (Bertini et al., 2018).

Overall, these findings show that visual processing for emotional stimuli in the absence of awareness is possible also in hemianopic patients without blindsight, i.e. hemianopic patients with performance at direct tasks at chance level. Moreover, these studies highlight many differences between the performance of hemianopic patients without affective blindsight (Anders, Birbaumer, Sadowski, Erb, Mader, Grodd, and Lotze, 2004; Anders, Eippert, Wiens, Birbaumer, Lotze, and Wildgruber, 2009; Bertini et al., 2013; 2017; Bertini et al., 2018; Cecere et al., 2014) and the performance of affective blindsight patients (De Gelder et al., 1999; de Gelder et al., 2001). Indeed, affective blindsight patients are able to discriminate between different emotional faces above the chance level and they also show response facilitation for emotionally–congruent pairs of facial stimuli (De Gelder et al., 1999; de Gelder et al., 2001; Pegna et al., 2005), regardless the type of emotion. On the contrary, hemianopic patients without affective blindsight show chance level performance when they have to discriminate between different emotional faces and they show a response facilitation only when a fearful face is presented in their blind visual field (Anders et al., 2004; 2009; Bertini et al., 2013; 2017; Bertini et al., 2018; Cecere et al., 2014). These differences seems to suggest that the subcortical retino-SC-Pulvinar-Amygdala circuit which has been proposed to subserve the implicit processing for emotional stimuli (Tamietto et al., 2012; Bertini et al., 2018) might be involved in mediating implicit visual abilities in both affective blindsight patients and hemianopic patients without affective blindsight. However, while the fear-specific implicit processing in hemianopic without blindsight might mainly rely on the activity of this subcortical pathway, it is possible that the peculiar implicit visual abilities of patients with affective blindsight involve also the contribution of other reorganized spared cortices (Gerbella, Caruana, and Rizzolatti, 2019). In line with this reasoning, the evidence reported so far suggest that patients with blindsight and hemianopic patients without blindsight might represent two distinct neuropsychological profiles, supported by the activity of different neural substrates. Specifically, the implicit visual processing demonstrated by

hemianopic patients without blindsight has been reported to be evident only in indirect task and to be limited to specific categories of stimuli, such as motion and fear. These specific stimuli are greatly relevant from an evolutionary perspective, since they might signal the presence of potential danger in the environment. Therefore, the ability to process these specific categories of stimuli in the absence of awareness has a great adaptive value and might reflect a useful mechanism, enabling efficient defensive responses in the presence of potential threat. Importantly, the processing of these specific categories of stimuli seems to involve the subcortical circuits conveying visual information from the retina to the SC and then projecting to the Pulvinar and Amygdala, which are relevant for processing threat-related information (Ledoux, 1998), and to the dorsal extra-striate areas, which are known to play a pivotal role in motion processing (Albright, 1984; Huk and Heeger, 2002).

On the other hand, in patients with blindsight that show evidence of implicit processing also in 2AFC and who demonstrate the ability of processing in the absence of awareness a wide range of different stimuli, these residual visual abilities seems to involve not only the contribution of the same subcortical SC-Amygdala and SC-dorsal extra-striate pathways proposed in mediating implicit abilities in patients without blindsight (Tamietto et al., 2012), but also the contribution of spared and functionally reorganized visual cortices. Such a peculiar functional reorganization might have different accounts, depending both on the etiology or the lesion site.

Indeed, in patient GY, one of the most famous and tested blindsight patients, such a functional reorganization might be the result of plastic changes occurring due to the early onset of his lesion (Celeghin, de Gelder, and Tamietto, 2015), possibly involving also interhemispheric contributions (Celeghin, Diano, de Gelder, Weiskrantz, Marzi, and Tamietto, 2017; Celeghin, Bagnis, Diano, Méndez, Costa, and Tamietto 2019). Again, the slow growth of a tumor in another well-documented case, i.e. patient DB, has might allowed profound plastic changes and, therefore, might account for his blindsight abilities (Duffau, 2017). Finally, affective blindsight has been mainly reported in a series of single case studies investigating patients with cortical blindness following bilateral occipital disruption (Pegna et al., 2005; Solcà, Guggisberg, Schnider, and Leemann, 2015; Burra, Hervais-Adelman, Celeghin, de Gelder, and Pegna, 2019; Striemer, Whitwell, and Goodale, 2019). In these patients, the disruption of both visual cortices might have induced a more radical reorganization of the visual pathways

conveying visual information from the subcortical structures to the cortex, thus promoting the emergence of their striking visual residual abilities. Overall, although the functional neuroanatomy of the affective blindsight still remain elusive, post-lesional plastic changes occurring to the subcortical V1-independent pathways and their multiple connections with extra-striate cortical areas, both within the dorsal and the ventral stream (Tamietto and Morrone, 2016), might represent a plausible account for this phenomenon. In this perspective, it has been recently proposed that in affective blindsight patients, facial emotional visual information is conveyed from the SC to the Pulvinar, from which it is directly projected to extra-striate and temporal cortices, such as the Superior Temporal Sulcus, to finally reach the Amygdala (Gerbella et al., 2019). This suggests a significant contribution of extra-striate areas at least in mediating the above chance performance in discriminating emotional faces and the facilitatory effects for congruent pairs of emotional stimuli, typical of patients with affective blindsight.

1.3. Cortical asymmetries in visuospatial abilities

Neuropsychological findings regarding the behavioral consequences of brain lesions have provided evidence for the presence of cortical asymmetries in the visuospatial abilities. Specifically, in the spatial hemineglect syndrome patients fail to be aware of stimuli presented in the contralesional part of the visual field and show a distorted representation of the left part of space and objects. Spatial hemineglect is caused by lesions to frontal, parietal, or sub-cortical structures, and it is more common and severe after a right lesion compared to a left lesion, suggesting the presence of a cortical asymmetry in the higher-order representation of the visual field (Bisiach and Luzzatti, 1978; Heilman, Valenstein, and Watson, 1984).

Similarly to neglect patients, also healthy participants show a slight but consistent spatial bias toward the left visual field. The tendency to overestimate the left compared to the right part of the visual field in healthy participants is commonly called “pseudo-neglect” (Bowers and Heilman, 1980). Even if the pseudo-neglect magnitude is smaller than the severe rightward bias seen in neglect patients, the pseudo-neglect is found with consistency across individuals and different experimental tasks (Jewell and McCourt, 2000). Indeed, the pseudo-neglect was found in both line bisection and Greyscales tasks, therefore affecting both the perception of length (McCourt and Olafson, 1997) and brightness across the horizontal axis of the visual field (Nicholls, Bradshaw, and Mattingley, 1999). Moreover, also size and numerosity

perception are modulated by the field of presentation, specifically these features are overestimated when presented in the left compared to the right visual field (Nicholls et al., 1999). Furthermore, neglect and pseudo-neglect seem to arise from the same neural organization, because same experimental modifications induce same modulation of the spatial bias. Specifically, both neglect and pseudo-neglect biases are modulated in the same direction by stimulus length, position along the horizontal and vertical midlines of the visual field and viewing distance (McCourt and Jewell, 1999; Riddoch and Humphreys, 1983; McCourt and Garlinghouse, 2000).

The observed asymmetry in the visuospatial representation has long been related to the right hemisphere specialization in the control of spatial attention, but the mechanisms behind the asymmetry between right and left hemispheres have not been yet elucidated (Howseman, Zeki, and Mesulam, 1999; Gitelman, Nobre, Parrish, LaBar, Kim, Meyer, and Mesulam, 1999). Two classical theories tried to interpret the strong asymmetry in the incidence of spatial hemineglect after right compared to left hemisphere lesions, the Heilman's hemispatial theory (Heilman and Van Den Abell, 1980; Heilman and Valenstein, 1979) and the Kinsbourne's opponent processor model (Kinsbourne, 1977). The Heilman's hemispatial theory claim that the right hemisphere is able to represent both the contra- and ipsi-lateral visual hemifields, whereas the left hemisphere is only able to represent the contralateral (Heilman and Van Den Abell, 1980; Heilman and Valenstein, 1979). Consequently, a lesion of the left hemisphere is expected not to compromise the representation of the entire visual field, due to the ability of the spared right hemisphere to represent both hemifields. On the contrary, a lesion to the right hemisphere is expected to impair severely the higher-order representation of the entire visual field, because the spared left hemisphere is not able to represent concurrently both the contra- and ipsi-lateral visual hemifield. To the other side, the Kinsbourne's opponent processor model claim that each hemisphere has a natural visuospatial bias toward the contralateral hemifield, and that the left hemisphere bias toward the right hemifield is stronger than the right hemisphere bias toward left hemifield (Kinsbourne, 1977). Consequently, the bias of the two hemispheres are in balance in healthy subjects, due to the reciprocal inter-hemispheric inhibition. However, when a brain lesion occurs, the spared hemisphere contralateral bias stops to be counterbalanced by the other hemisphere bias. Therefore, the impairment in the representation of one affected hemifield also results in the over activation of the spared

hemifield. A lesion of the left hemisphere is expected not to compromise strongly the higher-order representation of the visual field, because the right hemisphere bias toward the left hemifield is not particularly remarkable. On the contrary, a lesion to the right hemisphere is expected to severely impair the higher-order representation of the entire visual field, because of the strong bias of the spared left hemisphere toward the right hemifield.

In one of the more complete and investigated model, Corbetta and Shulman (Corbetta and Shulman, 2002; 2011) have proposed a functional and anatomical model of attentional control that accounts for the hemispheric asymmetries. Specifically, this model describe the attentional system as the interaction of two different networks: a bilateral dorsal fronto-parietal network, which includes the Frontal Eye Field (FEF) and Posterior Parietal cortex, and a right-lateralized ventral fronto-parietal network, which includes the Temporo-Parietal junction and ventral Frontal cortex. The bilateral dorsal fronto-parietal network is involved in the endogenous shifts of spatial attention and the following top-down modulation of sensory areas. To the other side, the right-lateralized ventral fronto-parietal network is involved in the exogenous disengaging of spatial attention when a salient stimulus occurs. According to authors, the hemispatial neglect is expected to be caused by a lesion to the right-lateralized ventral fronto-parietal network, suggesting that the hemispatial neglect arise from the impairment of the attentional system involved in the exogenous reorienting of spatial attention. Because the ventral fronto-parietal network is right-lateralized, hemispatial neglect is expected to arise after a right lesion.

The asymmetry found between the left and the right hemifields is well correlated with the asymmetry found between the right and left hemispheres in the representation of space and control of spatial attention. A transcranial magnetic stimulation (TMS) on the right parietal cortex or right FEF is able to induce a rightward bias in a line bisection task, whereas the same TMS pulse on the left parietal cortex or left FEF has no effect (Fierro, Brighina, Oliveri, Piazza, La Bua, Buffa, and Bisiach, 2000; Brighina, Bisiach, Piazza, Oliveri, La Bua, Daniele, and Fierro, 2002). Again, in a bilateral partial report paradigm, TMS to the right parietal cortex was able to decrease the accuracy to recall target presented in the left hemifield while increase the accuracy to recall target from the right hemifield. In a following study, the same spatial bias has found with the TMS of right frontal cortex. However, no TMS modulation was found after both left parietal or frontal stimulation (Hung, Driver, and Walsh, 2005;

2011). Asymmetry between right and left hemispheres are present also in common spatial orienting task, i.e. classical Posner tasks. A TMS during the delay between the spatial cue and the target presentation induces different modulation when is applied to the right compared to the left FEF. Specifically, a single pulse of TMS to the FEF is able to cancel out the common reaction time enhancement for valid compared to invalid trials, i.e. faster reaction times when the cue and target location are congruent than when they are incongruent. But if the TMS over the left FEF cancel out the enhancement only for target presented in the right contralateral hemifield, the TMS to the right FEF cancels out the validity effect for target presented in both hemifield (Grosbras and Paus, 2003; Chanes, Chica, Quentin, and Valero-Cabré, 2012; Duecker, Formisano, and Sack, 2013). Similar results were found with imaging data, specifically the right superior Parietal lobe was found responding with distinct responses when attention was directed to left and right visual field (Corbetta, Miezin, Shulman, and Petersen, 1993; Nobre, Sebestyen, Gitelman, Mesulam, Frackowiak, and Frith, 1997). The right dominance in the visuospatial representation is also supported by a DTI study, where the three main parieto-frontal white matter tracts were analyzed. First, a dorsal to ventral gradient of lateralization of the superior longitudinal fasciculi volumes was found, where the more dorsal fasciculus shows the same volume between the right and the left hemisphere while the more ventral shows a greater volume for the right branch compared to the left one. Moreover, only the volume of the right branch of the superior longitudinal fasciculi correlates with asymmetry in the behavioral performance to visuospatial tasks. Specifically, the volume of the right fronto-parietal fasciculi predicted the distribution of both the magnitude of pseudo-neglect in the line bisection task and the reaction times to left compared to right targets in a Posner task (de Schotten, Dell'Acqua, Forkel, Simmons, Vergani, Murphy, and Catani, 2011). Overall, the right hemisphere shows a peculiar and strong dominance over the left hemisphere in the control of spatial attention and more general visuospatial representation that produces a small but consistent preference for the left compared to the right hemifield. This subtle but consistent phenomena in healthy participants is enhanced when a brain lesion targets the right hemisphere compared to the left one by resulting in the neglect syndrome. Due to the strict relationship between the visual perception and attention networks in building a coherent representation of the visual space, hemispheric asymmetries are important to be investigated.

1.4. Electrophysiological correlates of the functionality of the visual system

Electroencephalogram (EEG) recordings might represent a useful tool to investigate the electrophysiological correlates of the functioning of the visual system after posterior brain lesions, inducing visual field defects. For instance, several studies have investigated electrophysiological activity evoked by stimuli presented in the blind field. However, the majority of these investigations focused on the study of visually-evoked potentials (VEPs) and failed in recording from the lesioned hemisphere robust and consistent VEPs responses evoked by the presentation of stimuli in the blind visual field (Bollini, Sanchez-Lopez, Savazzi, and Marzi, 2017; Dundon, Bertini, Làdavas, Sabel, and Gall, 2015; Grasso, Làdavas, and Bertini, 2016; Kavcic, Triplett, Das, Martin, and Huxlin, 2015). The lack of any VEPs response in the lesioned hemisphere for unseen stimuli is well documented in several studies that used simple flash stimuli or checkerboard pattern reversals (Brigell, Celesia, Salvi, and Clark-Bash, 1990; Celesia, Meredith, and Pluff, 1983; Onofrj, Bodis-Wollner, and Mylin, 1982) both when stimuli were presented separately in one of the hemifields or in simultaneously in both visual fields (Biersdorf, Bell, and Beck, 1992; Brigell et al., 1990; Celesia et al., 1983; Ffytche, Guy, and Zeki, 1996; Korogi et al., 1997; Onofrj et al., 1982). The residual neural activity for the processing of stimuli presented in the blind visual field might be too weak and degraded to be able to evoke an electrophysiological activity synchronized and consistent across trials. Indeed, the averaging processing to extract VEPs cancels out the contribution of any electrophysiological activity that is not synchronized in time and phase between trials.

Consequently, more recent investigations have exploited the oscillatory nature of the EEG signal by using visual stimulation that flicker at a brain-related frequency and by extracting from the EEG signal the different contribution of each brain-related oscillation. In this respect, the steady-state visually-evoked potentials (SSVEPs) are EEG responses to visual stimulation at specific frequencies and they are particularly useful because of the better signal-to-noise ratio and resistance to different kinds of artifacts (Di Russo, Teder-Sälejärvi, and Hillyard, 2003; Vialatte, Maurice, Dauwels, and Cichocki, 2010; Ding, Sperling, and Srinivasan, 2006; Norton, Umunna, and Bretl, 2017; Sharon and Nir, 2018). Accordingly, in a recent work, the presentation of simple visual stimuli in the blind field that flicker at 12 Hz evoked highly reliable SSVEPs similarly to those found for cortical extra-striate areas in healthy participants

(Sanchez-Lopez, Pedersini, Di Russo, Cardobi, Fonte, Varalta, Prior, Smania, Savazzi, and Marzi, 2019). On the other hand, the event-related spectral perturbations (ERSPs) reflect perturbations of the spontaneous rhythmic activity of the brain after the presentation of a stimulus across time and are particularly useful because they can grasp a reliable signal also on a trial-by-trial basis (Cohen, 2011). Indeed, studies investigating oscillatory patterns in response to unconscious visual stimuli have found significant ERSPs both in patients with blindsight (Del Zotto, Deiber, Legrand, De Gelder, and Pegna, 2013; Schurger, Cowey, and Tallon-Baudry, 2006; Tipura, Pegna, de Gelder, and Renaud, 2017) and in patients without blindsight (Grasso et al., 2018)

Interestingly, among all the spontaneous brain frequencies, alpha oscillatory activity (7-13 Hz) seems to represent well the complex interaction between the visual and attentional system in shaping the visual perception. First, alpha oscillations are the natural frequency range over the posterior occipito-parietal regions (Rosanova, Casali, Bellina, Resta, Mariotti, and Massimini, 2009). Moreover, the modulations of alpha oscillatory activity are commonly seen for the processing of visual stimuli (Pfurtscheller et al., 1994) and the allocation of spatial attention (Thut, Nietzel, Brandt, and Pascual-Leone, 2006; Capilla, Schoffelen, Paterson, Thut, and Gross, 2014), thereby suggesting an active role in shaping visual perception and spatial attention (Klimesch, Sauseng, and Hanslmayr, 2007; Jensen and Mazaheri, 2010). Furthermore, the modulation of posterior alpha activity can predict the perceptual fate of forthcoming visual stimuli (Ergenoglu, Demiralp, Bayraktaroglu, Ergen, Beydagi, and Uresin, 2004; Hanslmayr, Aslan, Staudigl, Klimesch, Herrmann, and Bäuml, 2007; van Dijk, Schoffelen, Oostenveld, and Jensen, 2008; Busch, Dubois, and VanRullen, 2009; Mathewson, Gratton, Fabiani, Beck, and Ro, 2009) and reflect variations in the excitability of the visual cortices both within (Romei et al., 2008a; Dugué, Marque, and VanRullen, 2011) and between participants (Romei, Rihs, Brodbeck, and Thut, 2008b), suggesting an active causal role in shaping the visual perception. In line, the modulation of alpha oscillatory activity reflects the modulation of the confidence level in visual discrimination tasks (Samaha, Iemi, and Postle, 2017; Benwell, Tagliabue, Veniero, Cecere, Savazzi, and Thut, 2017). Finally, the speed of alpha oscillations can account for the difference in the temporal resolution of the conscious visual experience across participants (Samaha and Postle, 2015).

In addition to the wide range of studies linking alpha oscillations to visual performance, oscillations in the alpha band (7-13 Hz) over occipito-parietal scalp regions are also the dominant frequency range of activity in the resting human brain (Berger, 1929) and alpha power at rest has been proposed to reflect the tonic and distributed synchronous activity of the underlying neurons (Klimesch et al., 2007; Sadaghiani and Kleinschmidt, 2016). Interestingly, the tonic alpha power measured during rest has been shown to be associated with subsequent task-related phasic changes in alpha activity and to be positively correlated to performance (Klimesch, 1997; Klimesch, 1999; Cecere, Rees, and Romei, 2015; Mathewson et al., 2009), therefore suggesting a link between efficient task execution and power in the alpha range during rest. This converging evidence suggest that alpha oscillations, also during resting-state, might represent a useful index of the functionality of the visual system.

Chapter 2: Posterior brain lesions selectively alter alpha oscillatory activity and predict visual performance in hemianopic patients

2.1. Introduction

Oscillations in the alpha band (7–13 Hz) over occipito-parietal scalp regions are the dominant frequency range of activity in the resting human brain (Berger, 1929, Rosanova et al., 2009). Reduced alpha oscillatory amplitude have been observed during the processing of perceived (Pfurtscheller et al., 1994) and unperceived (Grasso et al., 2018) visual stimuli and the allocation of visuospatial attention (Capilla et al., 2014; Rihs, Michel, and Thut, 2009; Thut et al., 2006), suggesting an active inhibitory function of oscillatory amplitude in this frequency band in shaping visual perception and spatial attention (Jensen and Mazaheri, 2010; Klimesch et al., 2007). Accordingly, the posterior alpha amplitude has been reported to predict the perceptual fate of forthcoming visual stimuli (Dijk et al., 2008) and to reflect variations in the excitability of the visual cortices (Romei et al., 2008a; Romei et al., 2008b). On the other hand, the frequency of the oscillations in the alpha band has been proposed to reflect a mechanism of perceptual sampling, suggesting that the individual alpha frequency (IAF) might represent a measure of temporal resolution for information processing (Cecere et al., 2015; Klimesch et al., 2007; Valera, Toro, John, and Schwartz, 1981). Moreover, recent studies have related the IAF to the cyclic gating of visual perception, showing a direct link between IAF and visual sampling rate (Samaha and Postle, 2015).

Thus, converging evidence show that alpha oscillatory frequency and amplitude represent indices of the posterior cortices' functionality and, hence, of the visual system even at rest (Bonnard, Chen, Gaychet, Carrere, Woodman, Giusiano, and Jirsa, 2016). Therefore, posterior brain lesions disrupting the neural circuits of the visual system and inducing visual field defects, shall result in altered alpha activity. Alterations in alpha oscillations have been previously described in a range of neurological and psychiatric disorders (Babiloni, Frisoni, Pievani, Toscano, Del Percio, Geroldi, Eusebi, Miniussi, and Rossini, 2008; Dunkley, Da Costa, Bethune, Jetly, Pang, Taylor, and Doesburg, 2015; Gawel, Zalewska, Szmidt-Sałkowska, and Kowalski, 2009; Montez, Poil, Jones, Manshanden, Verbunt, van Dijk, and Brussaard, 2009; Sponheim, Clementz, Iacono, and Beiser, 2000). Yet, studies on brain-lesioned patients have provided rather sparse evidence on the remapping of oscillatory

patterns following brain damage. Although a clear increase in low frequency (delta/theta) oscillatory activity has been described in perilesional areas, reports in the alpha range are rather inconsistent (Butz, Gross, Timmermann, Moll, Freund, Witte, and Schnitzler, 2004; Chu, Braun, and Meltzer 2015; Dubovik, Pignat, Ptak, Aboulafia, Allet, Gillabert, and Magnin, 2012; Laaksonen, Helle, Parkkonen, Kirveskari, Mäkelä, Mustanoja, Tatlisumak, Kaste, and Forss, 2013; Tecchio, Zappasodi, Pasqualetti, Tombini, Salustri, Oliviero, Pizzella, Vernieri, and Rossini, 2005; Visser, Wieneke, VanHuffelen, DeVries, and Bakker, 2001; Westlake, Hinkley, Bucci, Guggisberg, Findlay, Henry, Nagarajan, and Byl, 2012).

The highly variable lesion profile (including anterior and posterior brain lesions) of the clinical populations tested in previous studies might account for such inconsistent evidence. Indeed, significant alterations in the alpha range shall be expected after damage of posterior (but not anterior) regions of the brain, given their prominent role as alpha generators (Bollimunta, Chen, Schroeder, and Ding, 2008; Thut, Veniero, Romei, Miniussi, Schyns, and Gross, 2011). In contrast, oscillations have been mainly studied in patients with lesions involving the territory of the middle cerebral artery (Chu et al., 2015; Dubovik et al., 2012; Laaksonen et al., 2013; Westlake et al., 2012), thus preventing investigations on the specific impact of posterior lesions on the alpha oscillatory patterns. To investigate whether lesions of the posterior (but not anterior) brain regions might specifically affect activity in the alpha range, we recorded EEG activity during eye-closed resting state in patients with posterior lesions, in a group of control patients with more anterior lesions and in a group of age-matched healthy controls. We hypothesize that posterior lesions only will affect oscillations in the alpha range with a reduction both in the alpha frequency peak and amplitude. Moreover, due to the prominent role of the right hemisphere in visuospatial processing and in balancing the interhemispheric inhibition (Kinsbourne 1977), lesions to the right posterior cortices might induce stronger alpha dysfunction compared to lesions affecting the left hemisphere. In addition, since increased theta oscillatory activity has been reported in perilesional areas (Chu et al., 2015; Dubovik et al., 2012), theta frequency was also analyzed as a control, to test whether brain lesions might induce alterations also in this frequency range.

Finally, we investigated the link between alpha oscillations and visual performance using the Grayscales task (Mattingley, et al., 1994a; Mattingley et al., 2004), to test visuo-spatial representation in all participants. Crucially, we also tested whether alterations in alpha

oscillations could predict alterations in visual performance by using clinical measures of visual detection in the blind field of hemianopic patients (Bolognini, Rasi, Coccia, and Làdavas, 2005), both when patients were required to keep their gaze on a central fixation cross and when they were free to move their eyes to compensate for the visual field loss. Both in the Grayscales task and in clinical measures of visual detection we expect visual performance to correlate with indices of alpha activity, in line with a functional role of alpha oscillations in visual processing and visuo-spatial abilities.

2.2. Methods

2.2.1. Participants

Four groups of participants took part to the study: eleven patients (8 males, mean age = 50.7 years, mean time since lesion onset = 12.8 months) with visual field defect due to lesions to the left posterior cortices, ten patients with visual field defect due to lesions to the right posterior cortices (7 males, mean age = 56.1 years, mean time since lesion onset = 14.6 months), a control group of twelve patients without hemianopia with lesions to fronto-central and fronto-temporal cortices up to the limit of the post-central gyrus and of the anterior part of the temporal lobe (5 males, mean age = 45.8 years, mean time since lesion onset = 20.4 months). All the lesions of the patients in the control group spared the posterior cortices encompassing visually relevant areas. In addition, a control group of sixteen healthy participants (7 males, mean age = 54.1 years) was also tested. No differences between the groups were found relative to age ($F_{3,45} = 1.53$; $p = 0.220$) or time since lesion onset ($F_{2,30} = 0.70$; $p = 0.506$). Clinical details are reported in Table 1.

ID	Sex	Age	Onset	Lesion site	Visual Field Defect	Aetiology
EMI01	M	69	5	Left Occipital	Right hemianopia	Ischaemic
EMI02	M	45	7	Left Temporal	Right hemianopia	Hemorragic
EMI03	F	57	28	Left Fronto-Temporo-Insular	Right hemianopia	AVM
EMI04	M	50	7	Left Temporo-Occipito-Parietal	Upper right quadrantopia	Ischaemic
EMI05	M	81	9	Left Occipito-Temporal	Right hemianopia	Ischaemic
EMI06	M	51	5	Left Fronto-Temporo-Occipital	Right hemianopia	Abscess
EMI07	M	41	2	Left Occipital	Lower right quadrantopia	Ischaemic
EMI08	M	45	42	Left Fronto-Parieto-Temporal	Right hemianopia	Hemorragic
EMI09	F	29	26	Left Temporal	Upper right quadrantopia	AVM
EMI10	M	58	6	Left Temporo-Occipital	Right hemianopia	Ischaemic
EMI11	F	32	4	Left Parieto-Occipital	Right hemianopia	Ischaemic

EMI12	M	56	3	Right Occipital	Left hemianopia	Ischaemic
EMI13	F	38	13	Right Parieto-Occipital	Left hemianopia	Hemorragic
EMI14	F	37	4	Right Occipito-Temporo-Parietal	Left hemianopia	Tumor
EMI15	M	58	18	Right Temporo-Occipital	Left hemianopia	Ischaemic
EMI16	M	81	7	Right Occipital	Left hemianopia	Hemorragic
EMI17	M	51	4	Right Occipital	Left hemianopia	Tumor
EMI18	M	60	29	Right Temporo-Occipital	Left hemianopia	Ischaemic
EMI19	F	73	8	Right Temporo-Occipital	Left hemianopia	Ischaemic
EMI20	M	77	6	Right Fronto-Parietal	Left hemianopia	Hemorragic
EMI21	M	30	54	Right Temporal	Left hemianopia	Hemorragic
CON01	F	48	38	Left Fronto-Insular	No hemianopia	Ischaemic
CON02	F	44	40	Left Frontal	No hemianopia	Tumor
CON03	M	28	11	Left Fronto-Parietal	No hemianopia	Tumor
CON04	F	45	39	Left Frontal	No hemianopia	Tumor
CON05	F	46	12	Left Temporal Pole	No hemianopia	Hemorragic
CON06	M	62	7	Left Temporo-Insular	No hemianopia	Abscess
CON07	M	34	7	Left Frontal	No hemianopia	Tumor
CON08	F	57	5	Right Fronto-Insular	No hemianopia	AVM
CON09	M	42	59	Right Frontal	No hemianopia	Abscess
CON10	F	42	19	Right Frontal	No hemianopia	Tumor
CON11	M	51	3	Right Temporo-Insular	No hemianopia	Tumor
CON12	F	51	5	Right Temporal	No hemianopia	Tumor

Table 1. Summary of clinical data of all patients that took part to the study. Legend: M = Male; F = Female; AVM = Arteriovenous Malformation

Mapping of brain lesions was performed using MRIcro. Lesions documented by the most recent clinical CT or MRI were traced onto the T1-weighted MRI template from the Montreal Neurological Institute provided with MRIcro software (Rorden and Brett 2000; Rorden, Karnath, and Bonilha 2007) with the exception of EMI7 and EMI19, whose MRI scans were not available. Lesion volumes were computed for each patient and the extents of the lesions were compared between the three patients' groups, revealing no significant differences (one-way ANOVA, $F_{2,28} = 0.97$, $p = 0.391$) between hemianopic patients with left lesions, hemianopic patients with right lesions and control patients (see Fig. 2). Right-lesioned patients were screened for the presence of neglect using the Behavioral Inattention Test (Wilson, Cockburn, and Halligan 1987), to ensure performance was in the normal range. All patients showed normal or corrected-to-normal visual acuity. Patients were informed about the procedure and the purpose of the study and gave written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of

Helsinki and was approved by the Ethics Committee of the Regional Health Service Romagna (CEROM; n.2300).

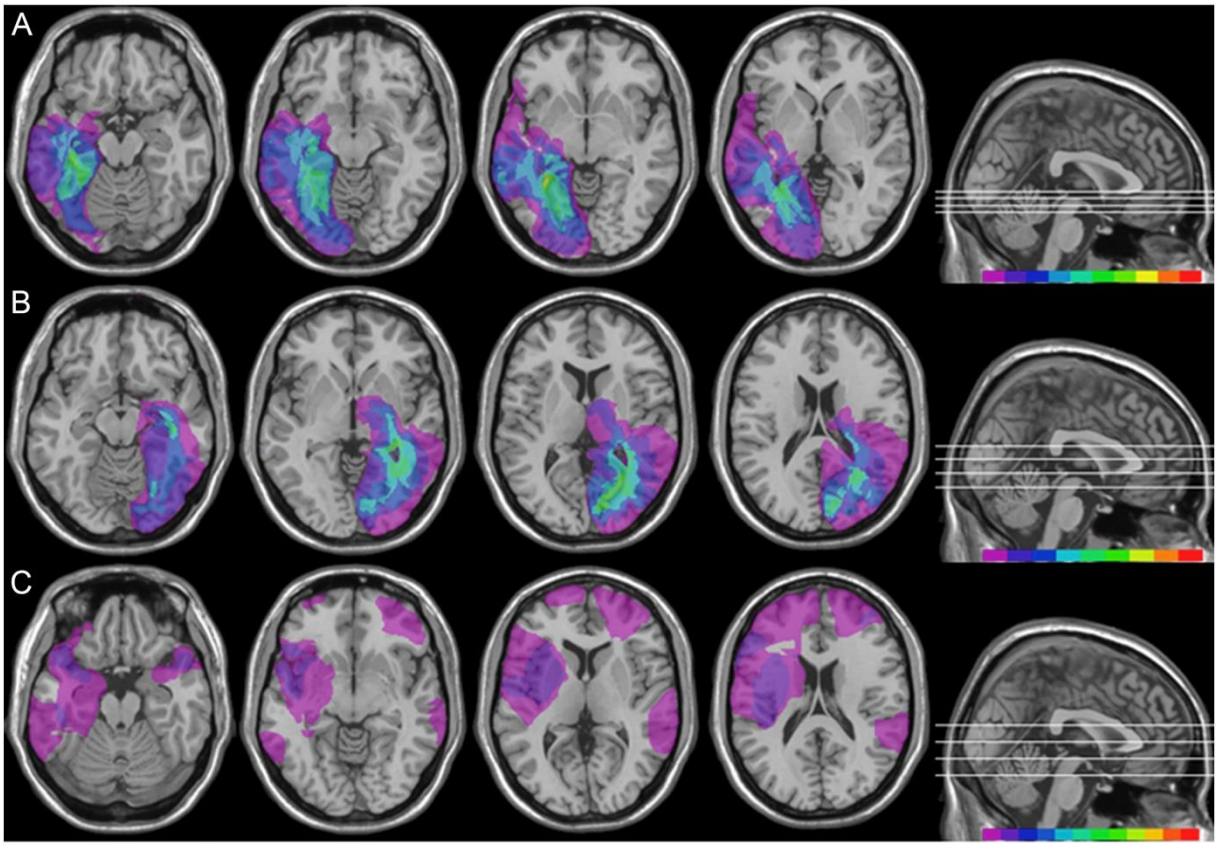

Figure 2. Location and overlap of brain lesions of patients. The image shows the lesions of the hemianopic patients with left posterior lesions (A), hemianopic patients with right posterior lesions (B) and control patients with anterior brain lesions (C) projected onto four axial slices of the standard MNI brain. In each slice, the left hemisphere is on the left side. The levels of the axial slices are marked by white lines on the sagittal view of the brain. The color bar indicates the number of overlapping lesions.

2.2.2. Experimental design

All the participants completed the Grayscales Task (see below), then underwent an EEG recording session during eyes-closed resting-state. In addition, all hemianopic patients completed two clinical tasks examining visual field disorders. The first task assesses the extent of the visual field defect and the second the ability to compensate for the visual field loss by eye-movements (see below). In order to probe the significance of the observed electrophysiological pattern for the visuospatial abilities of participants, a correlation between behavioral performance (i.e., Grayscales Task score for all participants and the

visual detection tests accuracy for the hemianopic patients) and electrophysiological activity was verified.

2.2.3. EEG during eye-closed resting-state

EEG signal was recorded from all participants while they seated in a sound-proof room at rest with their eyes closed. Each participant underwent five sessions of one-minute recording, to avoid drowsiness and related alterations in frequency and power as a function of time (Benwell, London, Tagliabue, Veniero, Gross, Keitel, and Thut, 2019). EEG data were recorded with a BrainAmp DC amplifier (BrainProducts GmbH, Germany) and Ag/AgCl electrodes (Fast'nEasy Cap, Easycap GmbH, Germany) from 59 scalp sites (Fp1, AF3, AF7, F1, F3, F7, FC1, FC3, FC5, FT7, C1, C3, C5, T7, CP1, CP3, CP5, TP7, P1, P3, P5, P7, PO3, PO7, O1, Fp2, AF4, AF8, F2, F4, F8, FC2, FC4, FC6, FT8, C2, C4, C6, T8, CP2, CP4, CP6, TP8, P2, P4, P6, P8, PO4, PO8, O2, FPz, AFz, Fz, FCz, Cz, CPz, Pz, POz, Oz) and the right mastoid. The left mastoid was used as reference, while the ground electrode was positioned on the right cheek. Vertical and horizontal electrooculogram (EOG) components were recorded from above and below the left eye, and from the outer canthus of both eyes. Data were recorded with a band-pass filter of .01–100 Hz and digitized at a sampling rate of 1000 Hz. The first 10 seconds of each one-minute recording session were excluded from the analysis, in order to avoid any confound due to the transition from the wakeful to the eye-closed resting-state. Impendences were kept under 10 KΩ. EEG recordings were off-line pre-processed and analyzed with EEGLAB (EEGlab version 4.1.1b; Delorme and Makeig 2004) and custom routines developed in Matlab (R2017a; The Mathworks Inc., USA). Data from all electrodes were re-referenced to the average of all scalp electrodes and filtered with a band-pass filter of 1–100 Hz. Continuous signals were segmented in epochs of 2 sec. After reducing data dimensionality to 32 components based on principal component analysis (PCA), components representing horizontal and vertical eye artifacts were visually identified and discarded. In order to compare the lesioned and intact hemispheres across participants, electrodes were swapped cross-hemispherically for patients with lesions to the right hemisphere. Thus, the data were analyzed as if all patients were left-lesioned. First, scalp

distribution of the mean alpha activity between 7 and 13 Hz, averaged across groups, was preliminarily visually inspected, revealing the highest alpha activity over parieto-occipital regions of the intact hemisphere and electrodes with the highest alpha power were selected. Specifically, six right parieto-occipital electrodes (P4, P6, P8, PO4, PO8, O2) were selected to represent the intact hemisphere (i.e., posterior region of the intact hemisphere). For the lesioned hemisphere, the corresponding homologue electrodes were selected (P3, P5, P7, PO3, PO7, O1; i.e., posterior region of the lesioned hemisphere). In addition, to test also for the oscillatory activity of anterior brain regions six fronto-central electrodes were selected for the intact (AF4, F2, F4, FC2, FC4, FC6; i.e., anterior region of the intact hemisphere) and lesioned hemisphere (AF3, F1, F3, FC1, FC3, FC5; i.e., anterior region of the lesioned hemisphere). The more anterior electrodes were excluded, to avoid contamination of the signal by the ocular artifacts. Moreover, electrodes on the sagittal and coronal midline were also excluded to provide a better segregation of the signal between the two hemispheres and between anterior and posterior regions.

From the cleaned EEG signal, we measured the individual alpha frequency (IAF), the amplitude of alpha oscillations (alpha power) and the amplitude of theta oscillations (theta power), as a control, separately for each participant. Specifically, an automated alpha peak detection routine (Corcoran, Alday, Schlesewsky, and Bornkessel-Schlesewsky, 2018) was first applied. The routine derived IAF for each channel in each region of interest. The routine was not able to identify the IAF in posterior regions for participants HEM02, HEM16, HEM17, CON05, HEALTHY15, HEALTHY16 and in anterior regions for participants HEM02, HEM16, HEM17, HEM18, CON03, CON05, CON06, HEALTHY06, HEALTHY09, HEALTHY12, HEALTHY13, HEALTHY15, HEALTHY16. This was probably due to the presence of low-powered peaks amid background noise (Corcoran et al., 2018). In that cases, the IAF was identified by a rater, blind to the purpose of the study, by visually inspecting the spectrogram, separately for each electrode. The mean IAF across groups was 9.36 Hz (range 6.92–13.00 Hz; see Fig. 3A).

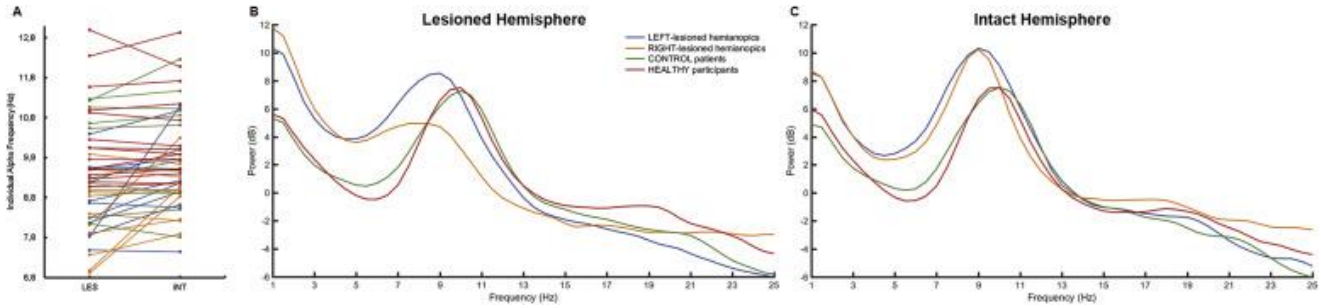

Figure 3. (A) Mean individual alpha frequency peaks in the posterior regions of interest during eye-closed resting state as measured in the lesioned (LES) and intact (INT) hemisphere are reported for each participant. (B–C) Spectrograms of the mean power across electrodes of the posterior region of interest in the lesioned and intact hemisphere.

An FFT on the 2-sec epochs was then computed, with a frequency resolution of 0.5 Hz (see Fig. 3B and C). Amplitude of alpha oscillations was calculated as the average power (in dB) in the window ± 1 Hz around the IAF, in each electrode. In addition, amplitude in the theta frequency was also analyzed as a control. The theta amplitude was calculated as the average power (in dB) between 4 and 6 Hz in each electrode. The subsequent statistical analyses were performed on IAF and alpha and theta power averaged between electrodes of the four regions on interest.

2.2.4. Grayscales Task

In order to test the visuospatial representation abilities in hemianopic patients, control patients and healthy controls, all participants underwent the Grayscales Task, shown to provide a reliable marker of visuospatial bias both in the clinical and healthy populations (Mattingley et al., 1994a; Mattingley et al., 2004). Accordingly, patients with hemianopia typically show a perceptual ipsilesional bias (Tant et al., 2002b), while healthy participants exhibit a leftward bias (Mattingley et al., 1994a; Mattingley et al. 2004). This perceptual asymmetrical performance has been attributed to a pattern of hemispheric function asymmetry (Tant et al., 2002b). In the Grayscales task, each stimulus consists of a pair of horizontal rectangles, one immediately above the other, presented on an LCD monitor. Each rectangle (height = 20 mm) was presented either in a short (width = 120 mm) and a long version (width = 260 mm), and was shaded continuously from black at one end to white at the other end. For each stimulus pair, one rectangle was darker at the right end and the other was darker at the left end (i.e., the two rectangles were mirror images of one another; see Fig. 6). Both rectangles within a pair had the same width. The entire task consists of 40 grayscale stimuli. The stimulus length

(long vs short) and orientation (left upper dark and right lower dark vs right upper dark and left lower dark) were evenly displayed. Stimulus presentation was pseudo-randomized and controlled by the experimenter.

Participants seated in a sound-controlled room in front of a 24″ LCD monitor (refresh rate: 60 Hz, 1920 × 1080 pixel resolution) at a viewing distance of 57 cm. Participants were asked to identify which of the two rectangles comprising each stimulus appeared darker overall by saying 'top' or 'bottom'. Participants could use eye-movements to explore the entire stimulus display and could respond without time constraints. No feedback on accuracy was provided during testing. Responses to each stimulus were categorized as left-biased when the participant selected the left darker end or right-biased when the participant selected the right darker end. An asymmetry score was then calculated (ipsilesional choices/trials number –0.5) to quantify the direction and magnitude of any perceptual bias. This score was derived by the normalization of the number of ipsilesional side choices. Specifically, the perceptual bias score could vary between −0.5, indicating the maximum bias towards the contralesional hemifield and +0.5, indicating the maximum bias to the ipsilesional hemifield. For healthy participants, a score of −0.5 would indicate a maximum bias towards the right hemifield and +0.5 a maximum bias towards the left hemifield. A score of zero, would account for absence of bias in a particular direction.

2.2.5. Visual detection tests

In order to investigate the severity of the visual field defect and the ability to compensate for the visual field loss by using eye-movements, all left- and right-lesioned hemianopic patients underwent a visual detection test under two conditions (Bolognini et al. 2005; Dundon et al. 2015; Grasso et al., 2016). In the Fixed-eyes condition, patients were not allowed to use eye-movements, thus the severity of visual field defect could be quantified, whereas in the Eye-movements Condition, patients were free to use eye-movements to detect visual targets, thus the ability to compensate for the visual field loss was measured. The apparatus for the visual detection examination consisted in a semicircular structure in which the visual stimuli were positioned. The apparatus was a plastic horizontal arc (height 30 cm, length 200 cm) fixed on the table surface. The visual stimulus consisted of the illumination of a red LED (luminance 90 cd/m^2 each), located horizontally at the subject's eye level, at an eccentricity of 8°, 24°,

40°, 56° in the blind and in the intact hemifield. A visual target was presented for 100 ms in different spatial positions, at 8°, 24°, 40° and 56° from either side of the central fixation point. Timing of stimuli was controlled by an ACER 711 TE laptop computer, using a custom program and a custom hardware interface (property of E.M.S. Medical. Details available at: http://www.emsmedical.net/applicazioni/medicina-fisica-riabilitativa/emianopsia). Two hundred trials were presented: 20 trials for each of the 8 visual positions and 40 trials in which no visual stimulus was presented, i.e., catch trials. The total number of trials was equally distributed in five blocks. Patients were instructed to press a response button after the detection of the targets and visual detection for each spatial position was recorded. D-prime (perceptual sensitivity) was calculated and used for the statistical analysis.

2.2.6. Statistical analysis

The oscillatory EEG patterns in the alpha and theta band during the eye-closed resting-state were analyzed. All the statistical analyses were performed using STATISTICA (StatSoft; Version 12.0; www.statsoft.com). To test whether posterior lesions might affect the oscillations in the alpha range, two separate ANOVAs for the IAF and alpha power were run. Each ANOVA had *Region* (posterior, anterior) and *Hemisphere* (intact hemisphere, lesioned hemisphere) as within-subject factors and *Group* (left-lesioned hemianopic patients, right-lesioned hemianopic patients, control patients, healthy participants) as a between-subjects factor. The same ANOVA was also run to analyze the power in the theta range. The Grayscales Task scores were analyzed with a one-way ANOVA with *Group* as a between factor (left-lesioned hemianopic patients, right-lesioned hemianopic patients, control patients, healthy participants). Performance of hemianopic patients in the visual detection tests (Fixed-eyes and Eye-movements conditions) was also analyzed. D-primes for each stimulus location of the blind field in the two visual detection tests were analyzed with two ANOVAs with *Group* as the between-subjects factor (left-lesioned hemianopic patients, right-lesioned hemianopic patients) and *Position* (8°, 24°, 40° and 56°) as the within-subject factor. When significant main effects or interactions were found, post-hoc comparisons were run with Tukey HDS test for unequal samples (Spjøtvoll and Stoline, 1973) and corrected p-values were reported. Further, we investigated the relationship between the participants' behavioral performance and alpha and theta activity with correlational analyses. Specifically, behavioral performance was correlated with the alpha parameters showing significantly different patterns

between groups, using Bonferroni-Holms corrections (corrected p-values are reported; Holm, 1979; Gaetano, 2018).

2.3. Results

2.3.1. Individual alpha frequency (IAF)

The overall ANOVA for the IAF revealed a significant *Region* x *Hemisphere* x *Group* interaction ($F_{3,45} = 2.87$, $p = 0.047$; see Fig. 4A). To explore this interaction, an ANOVA on IAF values over the posterior regions with *Hemisphere* (intact hemisphere, lesioned hemisphere) and *Group* (left-lesioned hemianopic patients, right-lesioned hemianopic patients, control patients, healthy participants) as factors was run. The ANOVA showed a significant main effect of *Group* ($F_{3,45} = 6.84$, $p < 0.001$) with slower posterior IAF both in left-lesioned (M = 9.05 Hz, p = 0.033) and right-lesioned (M = 8.62 Hz, p = 0.004) hemianopic patients relative to healthy participants (M = 10.29 Hz). In addition, the posterior IAF of right-lesioned hemianopic patients was also slower compared to control patients (M = 9.91 Hz; p = 0.037). No other significant difference was found (all ps > 0.22). The main effect of *Hemisphere* ($F_{1,45} = 14.17$, $p < 0.001$) was also significant, with the posterior IAF of the intact hemisphere (M = 9.74 Hz) being generally faster relative to the IAF of the lesioned hemisphere (M = 9.42 Hz, p = 0.002). Finally, these main effects are further explained by a significant interaction effect between *Group* and *Hemisphere* ($F_{3,45} = 3.43$, $p = 0.025$). More precisely, both left-lesioned and right-lesioned hemianopic patients showed a reduction of IAF in the lesioned hemisphere, relative to both the left and right hemisphere of healthy participants (all ps < 0.022). However, hemianopic patients with left lesions had a more selective slowing down of alpha oscillatory activity within the lesioned hemisphere only (M = 8.70 Hz), relative to the intact hemisphere (M = 9.40 Hz, p = 0.028), while hemianopic patients with right lesions showed no difference in IAF between the lesioned (M = 8.3 Hz) and the intact (M = 8.95 Hz; p = 0.065) hemispheres, therefore suggesting a significant slowing down of alpha oscillatory activity in both hemispheres. No other significant difference was found (all ps > 0.12; see Fig. 4B).

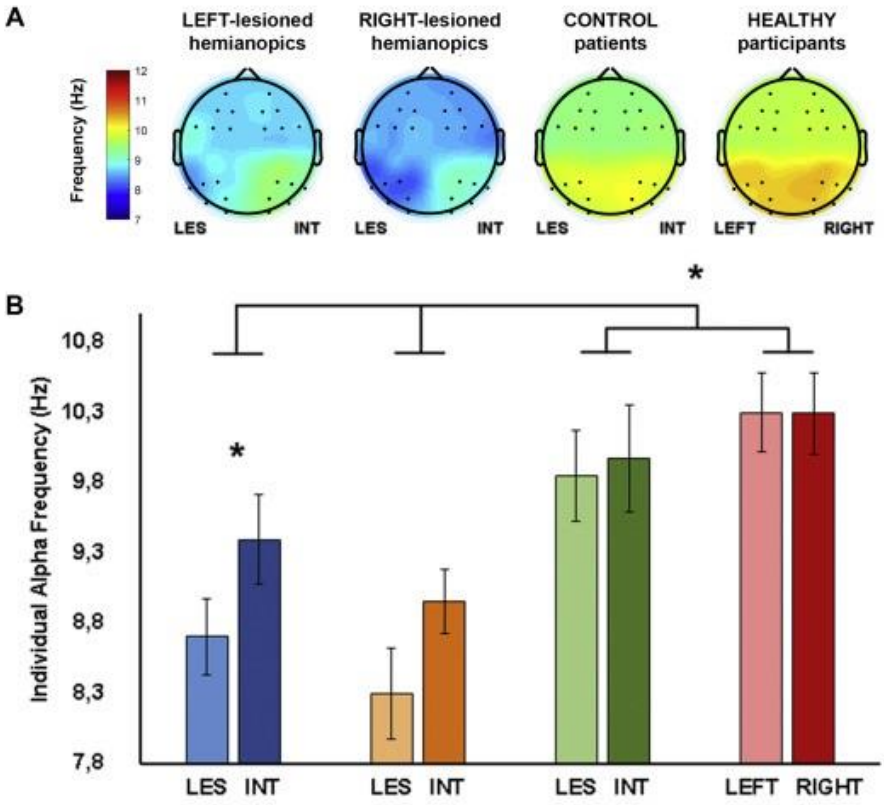

Figure 4. Individual alpha frequency during eye-closed resting-state. (A) Scalp topographies represent the scalp distribution of the individual alpha frequency in hemianopic patients with left posterior lesions, hemianopic patients with right posterior lesions, control patients with anterior lesions and healthy participants. The speed of alpha is color-coded such that faster alpha is associated with red color and slower alpha with blue color. For patients with lesions to the right hemisphere, electrodes were swapped cross-hemispherically, so that the lesioned hemisphere (LES) is represented on the left side. (B) Bar plots show mean alpha peak values in the posterior regions of the lesioned (LES) and intact (INT) hemispheres of patients and in the left and right hemispheres of healthy participants. Error bars represent SEM. Asterisks denote significant comparisons.

These findings are in line with our prediction that lesions occurring to the right posterior cortices might induce stronger and more generalized alpha dysfunction compared to lesions affecting the left hemisphere, due to the prominent role of the right hemisphere in perceptual visuo-spatial processing (Kinsbourne, 1977; Nicholls et al., 1999).

2.3.2. Alpha amplitude

The overall ANOVA for the alpha power revealed a significant *Region* x *Hemisphere* x *Group* interaction ($F_{3,45}$ = 12.86, p < 0.001; see Fig. 5A). A subsequent ANOVA considering the power over the posterior regions with *Hemisphere* (intact hemisphere, lesioned hemisphere) and *Group* (left-lesioned hemianopic patients, right-lesioned hemianopic patients, control patients, healthy participants) as factors was run to explore this significant interaction. The ANOVA did not show a significant main effect of *Group* ($F_{3,45}$ = 0.33, p = 0.806), but a

significant main effect of *Hemisphere* ($F_{1,45}$ = 31.06, p < 0.001), with higher posterior alpha power in the intact (M = 9.42 dB) relative to the lesioned hemisphere (M = 7.93 dB, p < 0.001). Importantly, a significant *Group* x *Hemisphere* interaction ($F_{3,45}$ = 9.50, p < .001) pointed to a reduced posterior alpha power for the lesioned relative to the intact hemisphere in both left- (M = 9.00 dB vs 11.075 dB, p = 0.050) and right- (M = 5.76 dB vs 10.13 dB, p < 0.001) lesioned hemianopic patients. By contrast, no significant difference was found between lesioned and intact hemisphere both in control patients (M = 8.62 dB vs 9.22 dB, p = 0.978) and healthy participants (left hemisphere: M = 8.034 dB vs right hemisphere: 7.99 dB, p = 1.00; Fig. 5B). No other significant difference was found (all ps > 0.496).

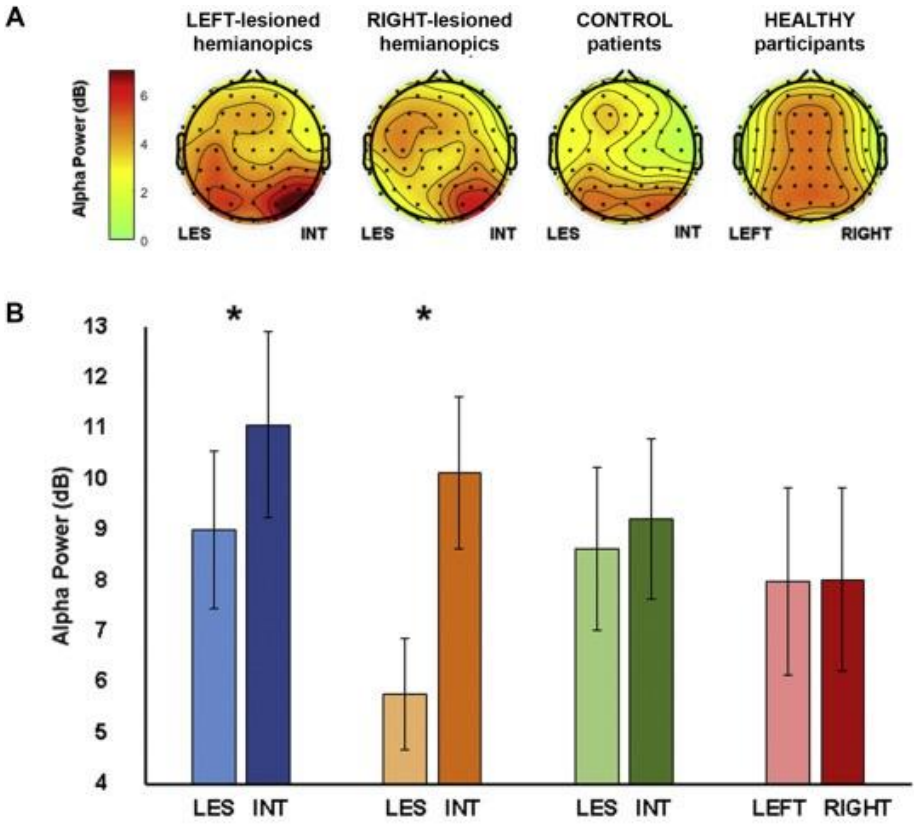

Figure 5. Alpha amplitude during eye-closed resting-state. (A) Scalp topographies represent the scalp distribution of the alpha power in hemianopic patients with left posterior lesions, hemianopic patients with right posterior lesions, control patients with anterior lesions and healthy participants. Alpha amplitude is color-coded such that higher alpha power is associated with red color and lower alpha power with green color. For patients with lesions to the right hemisphere, electrodes were swapped cross-hemispherically, so that the lesioned hemisphere (LES) is represented on the left side. (B) Bar plots show mean alpha power values in the posterior regions of the lesioned (LES) and intact (INT) hemispheres of patients and in the left and right hemispheres of healthy participants. Error bars represent SEM. Asterisks denote significant comparisons.

Since the interaction revealed an imbalance in alpha power in patients with posterior lesions, we measured the interhemispheric differences in alpha power (alpha power in the intact hemisphere minus alpha power in the lesioned hemisphere) to test whether lesions to the right hemisphere might induce a stronger interhemispheric alpha dysfunction. Indeed, right-lesioned hemianopic patients revealed a higher interhemispheric difference in alpha power (M = 4.37 dB) relative to left-lesioned hemianopic patients (M = 2.07 dB, p = 0.046; one-tailed t-test), in line with the hypothesis of a pivotal role of the right hemisphere in balancing interhemispheric inhibition.

2.3.3. Control analysis: alpha oscillations

Results so far have shown a selective slowing down of alpha oscillations together with a reduced amplitude of the alpha signal in the lesioned posterior sites of hemianopic patients only. Such parameters instead have been found unaltered in control patients when compared to healthy participants. However, it might still be the case that altered alpha activity might be dependent on the site of the lesion. If this was the case, alpha alterations could be found not only into hemianopic patients over posterior sites but also in the control patients' group over more anterior sites. To test this alternative hypothesis we have measured alpha frequency and power specifically at the site of the lesion, by means of ANOVAs with *Hemisphere* (intact hemisphere, lesioned hemisphere) and *Group* (left-lesioned hemianopic patients, right-lesioned hemianopic patients, control patients, healthy participants) as factors, in which we compared the alpha peak and power recorded over the electrodes of the lesioned regions in each group of patients (i.e., posterior regions in the left- and right-lesioned hemianopic patients and anterior regions in control patients). For the healthy controls group, the posterior regions were included in the analysis. In line with the previous results, the ANOVA on the IAF showed a significant main effect of *Group* ($F_{3,45} = 6.51$, $p < 0.001$), confirming that the alpha peak of both left- (M = 9.05 Hz, p = 0.029) and right- (M = 8.62 Hz, p = 0.003) lesioned hemianopic patients was slower compared to healthy participants (M = 10.29 Hz). In contrast, no significant difference was found between control patients (M = 9.42 Hz, p = 0.16) and healthy participants. More importantly, the interaction effect between *Group* and *Hemisphere* ($F_{3,45} = 4.00$, p = 0.013) was also significant, again showing that IAF was slower in the lesioned (M = 8.70 Hz) compared to the intact hemisphere (M = 9.40 Hz, p = 0.022) only in the left-lesioned hemianopic patients, but showing no difference between lesioned (M = 8.3

Hz) and intact (M = 8.95 Hz) hemisphere in right-lesioned hemianopic patients (p = 0.052) and control patients (M = 9.4 Hz vs 9.43 Hz; p = 1.00) or between the left (M = 10.29 Hz) and the right (M = 10.3 Hz) hemisphere in healthy participants (p = 1.00).

Similarly, the ANOVA on the alpha power confirmed the previous results, showing a significant *Group* x *Hemisphere* interaction ($F_{3,45}$ = 13.71, p < 0.001). Post-hoc comparisons revealed reduced alpha power for the lesioned relative to the intact hemisphere in both left- (M = 9.00 dB vs 11.075 dB, p = 0.033) and right- (M = 5.76 dB vs 10.13 dB, p < 0.001) lesioned hemianopic patients. Notably, considering the anterior region damaged in control patients, no significant difference was found between the lesioned and intact hemisphere in this group (M = 6.3 dB vs 5.65 dB, p = 0.95). Moreover, no significant difference was found between the left and right hemisphere in healthy participants (M = 8.027 dB vs 7.99 dB, p = 1.00). No other significant difference was found (all ps > 0.457).

Overall, these control analyses provided further support to the hypothesis that post-lesional changes in the alpha oscillatory patterns are specifically associated to posterior cortices' lesions.

2.3.4. Control analysis: theta oscillations

The previous analyses have shown that altered oscillatory patterns in the alpha range can be found after posterior but not anterior brain lesions. Since increased theta oscillatory activity in perilesional areas has also been reported in patients with brain damage (Butz et al., 2004; Chu et al., 2015; Dubovik et al., 2012; Laaksonen et al., 2013; Tecchio et al., 2005), enhanced theta power is expected both in patients with posterior and anterior brain lesions at the site of the lesion, therefore independently of whether the lesion is posterior or anterior.

The overall ANOVA for the theta power revealed a significant main effect of *Region* ($F_{1,45}$ = 9.35, p = 0.004), explained by higher theta power in the posterior regions (M = 1.5 dB) than in the anterior regions (M = 2.73 dB; p = 0.002), and a significant main effect of *Hemisphere* ($F_{1,45}$ = 35.75, p < .001), with higher theta power in the lesioned (M = 2.54 dB) relative to the intact hemisphere (M = 1.76 dB, p < 0.001). More importantly, the interaction *Hemisphere* x *Group* was also significant ($F_{3,45}$ = 3.41, p = 0.025). Post-hoc comparisons showed a significant increase in theta power in the lesioned hemisphere relative to the intact hemisphere in left-lesioned hemianopic patients (M = 4.00 dB vs 3.05 dB; p = 0.047), in right-lesioned

hemianopic patients (M = 4.47 dB vs 3.13 dB; p = 0.002) and in control patients (M = 1.56 dB vs 0.62 dB; p = 0.035). No difference in theta power between the left (M = 1.06 dB) and the right (M = 0.89 dB; p = 0.996) hemisphere was found in healthy participants. No other significant difference was found (all ps > 0.24).

Overall, this analysis showed that theta power is systematically enhanced (and not reduced as in the case of alpha power) in the lesioned hemisphere. Such effect is independent on whether the lesion is posterior or anterior as it was instead the case for alpha power which was selectively reduced following posterior (but not anterior) lesions.

2.3.5. Grayscales Task

Next, we looked at whether indices of oscillatory activity (in the alpha and theta band) could account for visual performance. First, we explored behavioral differences between groups in the Grayscales task. The one-way ANOVA on the magnitude of bias score in the Grayscales Task showed a significant main effect of *Group* ($F_{3,45}$ = 4.24, p = 0.010), but no post-hoc comparison reached significance (all ps > 0.07). However, on average, both left- (M = 0.31) and right-lesioned (M = 0.30) hemianopic patients showed a higher ipsilesional bias score compared to both healthy participants (M = 0.08) and control patients (M = 0.06; see Fig. 6).

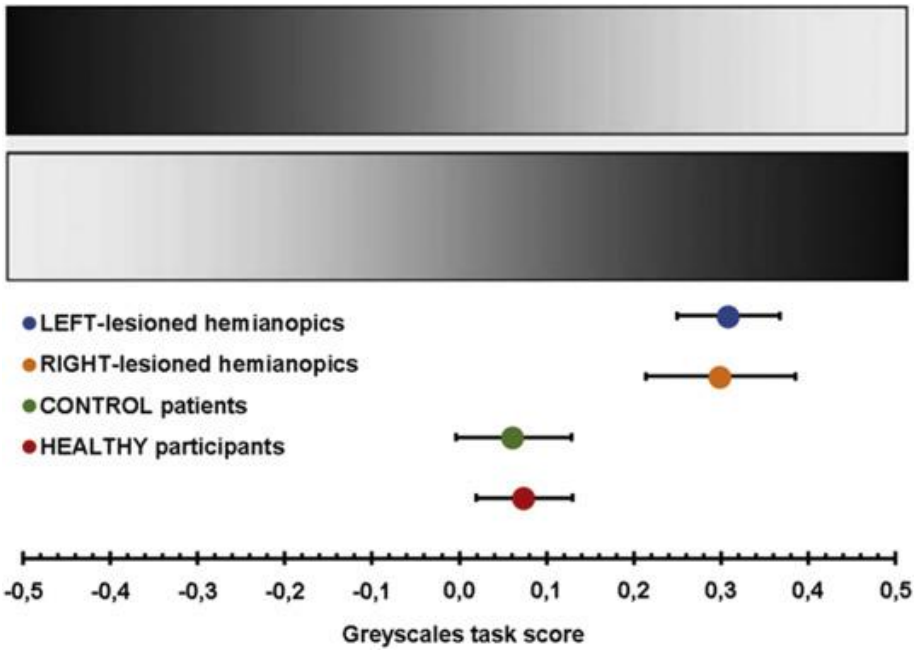

Figure 6. Grayscales task. The upper panel represents an example of stimuli used in the Grayscale task. The scatterplot in the lower panel shows the mean Grayscales task scores in each group. A score of −0.5 indicates the maximum bias towards the contralesional hemifield, while a score of +0.5 indicates the maximum bias to the ipsilesional hemifield. For healthy participants, a score of −0.5 indicates a maximum bias towards the right hemifield and +0.5 a maximum bias towards the left hemifield. A score of zero accounts for absence of bias in a particular direction.

Further, we investigated whether there was a relationship between participant's visuospatial bias and alpha activity. We found a negative correlation between posterior IAF and the bias score ($R_{49} = -0.34$, $p < 0.001$), i.e., the lower the posterior IAF the higher the bias towards the ipsilesional intact visual field (Fig. 7A). Moreover, a positive correlation between the interhemispheric differences in posterior alpha power and the bias score ($R_{49} = 0.51$, $p = 0.034$) was found, suggesting that the higher the interhemispheric imbalance of posterior alpha power towards the intact hemisphere, the higher the Grayscales Task bias towards the ipsilesional intact visual field (see Fig. 7B). Finally, in order to verify that only alpha activity is involved in visuo-spatial abilities, the relationship between participant's visuospatial representation and their oscillatory theta activity was also investigated. As expected, no significant correlation between the bias score and theta power imbalance was found ($p = 0.816$).

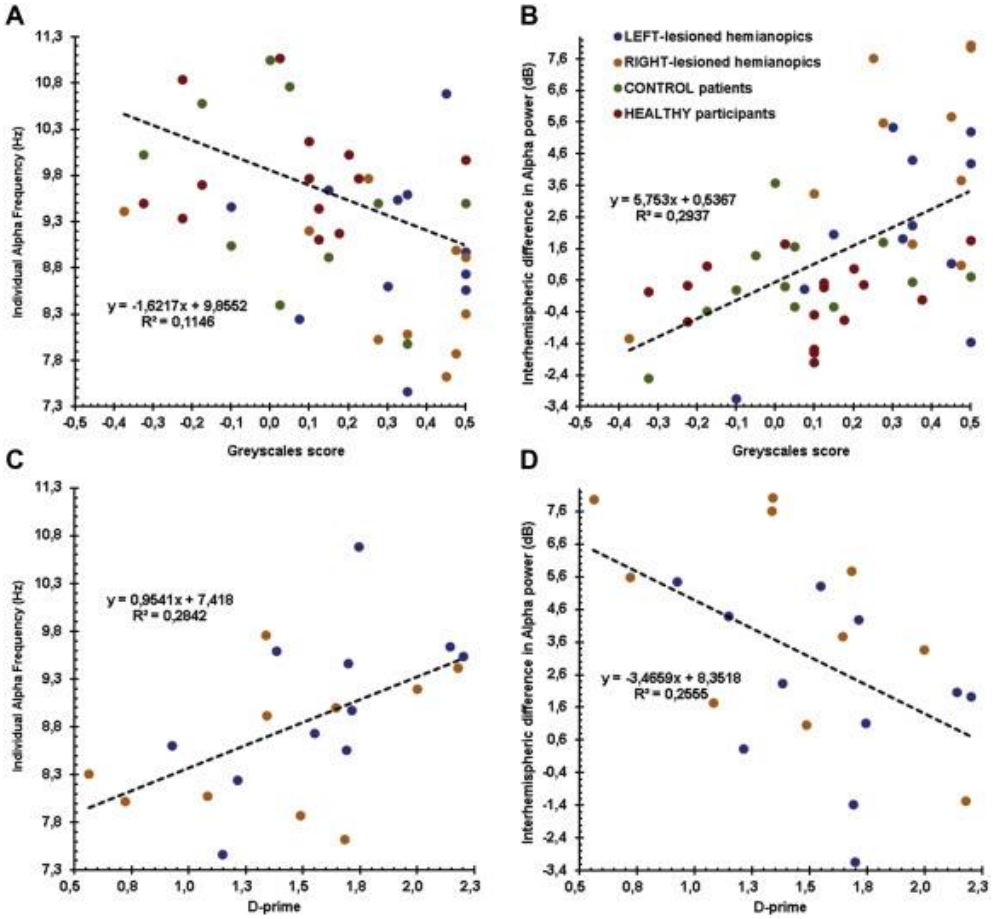

Figure 7. Upper panels depict correlations between the Grayscales task scores and individual alpha frequency (A) and the interhemispheric difference in alpha power (B). Lower panels depict correlations between mean perceptual sensitivity in the blind field in the Visual detection test in the Eye-movements condition (d-prime) and individual alpha frequency (C) and the interhemispheric difference in alpha power (D).

2.3.6. Visual detection tests

Finally, we further tested in hemianopic patients whether altered oscillatory activity in the alpha band can account for their behavioral performance in visual detection tests routinely used in clinical evaluations (Bolognini et al., 2005; Dundon et al., 2015; Grasso et al., 2016). Considering the visual detection test in the Fixed-eyes condition, the ANOVA for the d-prime values of left- and right-lesioned hemianopic patients showed a significant main effect of *Position* ($F_{3,57}$ = 7.80, p < 0.001). The post-hoc analysis showed that the d-prime for the stimuli presented at 8° (M = 1.09) was significantly greater compared to stimuli presented at 40° (M = 0.62, p = 0.022) and 56° (M = 0.34, p < 0.001) No other significant difference was found (all ps > 0.055; see Fig. 8A). No main effect of *Group* nor interaction *Group* x *Position* reached significance (all ps > 0.642).

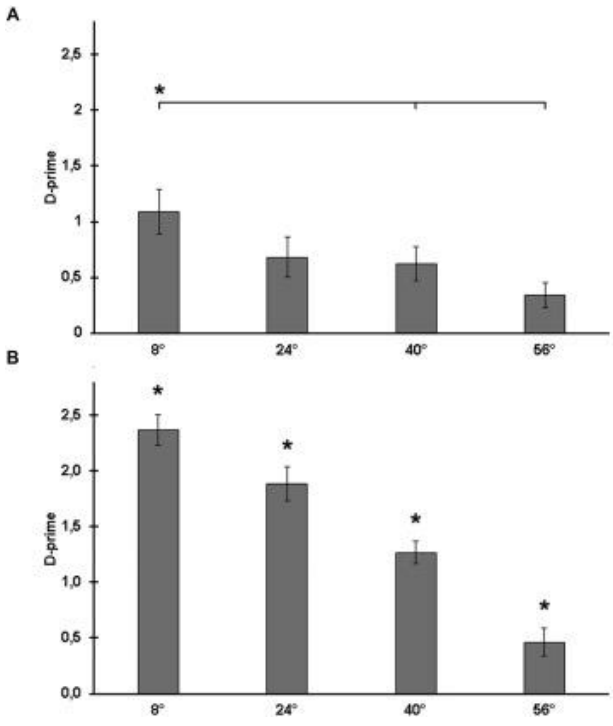

Figure 8. Visual detection tests. Mean d-prime for each of the four stimulus locations in the blind field (8°, 24°, 40° and 56°) for the visual detection tasks in the Fixed-eyes condition (A) and in the Eye-movements condition (B). Error bars represent SEM. Asterisks denote significant comparisons.

Next, the relationship between hemianopic patients' perceptual sensitivity in their blind field in Fixed-eyes condition and their posterior alpha activity was investigated to assess if posterior alpha activity measured for a given subject predicts the extent to which they show

an impairment in detection of visual stimuli when they were not allowed to move their eyes to compensate for the loss of visual field. No significant correlation between the mean d-prime for all the positions in the blind field and posterior alpha peak ($p = 0.423$) or alpha power imbalance ($p = 1.00$) was found. Further, no significant correlation between perceptual sensitivity in their blind field in Fixed-eyes condition and theta power imbalance was found ($p = 0.107$).

Relative to the visual detection test in the Eyes-movement condition, the ANOVA for the d-prime values showed a significant main effect of *Position* ($F_{3,57} = 70.37$, $p < .001$). The post-hoc analysis showed that d-prime for stimuli presented at 8° ($M = 2.37$) was significantly greater compared to stimuli presented at 24° ($M = 1.89$, $p = 0.005$), at 40° ($M = 1.27$, $p < 0.001$) and 56° ($M = 0.46$, $p < .001$). Furthermore, d-prime for stimuli presented at 24° was significantly greater compared to stimuli presented at 40° ($p < 0.001$) and 56° ($p < 0.001$). Finally, d-prime for stimuli presented at 40° was significantly greater compared to stimuli presented at 56° ($p < 0.001$; see Fig. 8B). Again, no main effect of *Group* nor interaction *Group* x *Position* was significant (all ps > 0.38). As in the previous task, the relationship between the perceptual sensitivity in their blind field in the Eyes-movement condition and posterior alpha activity was investigated. The mean d-prime for all the positions in the blind field showed a significant positive correlation with posterior IAF ($R_{21} = 0.53$, $p = 0.039$; Fig. 7C), suggesting that faster alpha is predictive of better performance, and a significant negative correlation with the posterior alpha power imbalance between hemispheres ($R_{21} = -0.51$, $p = 0.039$), suggesting that the higher the alpha power imbalance, the lower the perceptual sensitivity in the Eyes-movement condition (see Fig. 7D). Finally, no significant correlations between the perceptual sensitivity in the Eyes-movement condition and theta power imbalance was found ($p = 0.674$). Thus, posterior alpha activity can predict performance in perceptual sensitivity when patients are allowed to use eye-movements to compensate for their visual field loss.

2.4. Discussion

Posterior brain lesions can selectively impair oscillatory activity in the alpha range at rest while lesions to anterior regions do not significantly affect alpha oscillatory patterns. The present findings reveal that hemianopic patients with posterior lesions show both a selective

reduction of the IAF and alpha amplitude. This suggests that both left and right posterior lesions disrupt the neural circuits of the visual system, impairing its global functioning in the alpha range. Specifically, after posterior lesions, the IAF in both the intact and the lesioned hemispheres is reduced, which might reflect a general slowdown of the speed of processing in the visual system. Moreover, hemianopic patients show a reduced alpha power in the lesioned hemisphere, resulting in an imbalanced oscillatory alpha activity between the two hemispheres, which suggests an altered interhemispheric functioning in the alpha range.

Converging evidence show a central role of low-level visual cortices, such as V1 (Bollimunta et al., 2008), in coordinating and propagating alpha oscillations in the visual system (Hindriks, Woolrich, Luckhoo, Joensson, Mohseni, Kringelbach, and Deco, 2015). Specifically, it has been proposed that during resting-state, alpha oscillations propagate from lower to higher-order visual areas, providing a default organization of the visual system (Hindriks et al., 2015). This seems in line with the present observation that focal lesions to low-level visual cortices have detrimental effects on the organization and the interdependent and connected functioning of the visual system of the two hemispheres. In this perspective, oscillatory activity in the alpha range might reflect one of the functional mechanisms operating to keep the activity of the posterior cortices of the two hemispheres in balance. This is in agreement with influential models proposing that the posterior cortices of the two hemispheres competitively interact via interhemispheric inhibition to control visuospatial processing in the contralateral hemifields (Kinsbourne, 1977).

Importantly, we found that damage to the right posterior cortices induces more severe alterations of the oscillatory activity in the alpha range, relative to damage to left posterior cortices, suggesting a functional asymmetry between the two hemispheres. Indeed, hemianopic patients with right lesions show a similar reduction of the IAF in both the intact and lesioned hemisphere, while in hemianopic patients with left lesions, the right intact hemisphere maintains a higher IAF, compared to the left lesioned hemisphere. Similarly, right-lesioned, relative to left-lesioned, hemianopic patients show a stronger interhemispheric imbalanced alpha power. This indicates that both right and left lesions to the posterior cortices globally affect activity in the alpha range, but right posterior lesions have more detrimental effects in reducing the speed of processing in the alpha range in both hemispheres and in altering the interhemispheric distribution of the alpha amplitude. This finding is in agreement

with longstanding theories proposing a dominance of the right hemisphere in spatial representation (Heilman and Van Den Abell, 1980) and in balancing the interhemispheric inhibition (Kinsbourne, 1977). Notably, evidence concerning the dominance of the right hemisphere are based on functional asymmetries observed in posterior parietal cortices and fronto-parietal networks (Corbetta and Shulman, 2002; 2011). In addition, the theories assuming a prominent role of the right hemisphere in visuospatial processing have been widely influenced by established clinical findings on the prevalence of spatial neglect after right hemisphere damage (Bisiach, Pizzamiglio, Nico, and Antonucci, 1996; Halligan, Fink, Marshall, and Vallar, 2003; Milner and McIntosh, 2005; Robertson, 2001). However, the lesions of the patients tested in this study involve mainly the occipito-temporal cortices and patients do not show clinical signs of neglect. This pattern of lateralized results suggests that lesions to low-level visual cortices might alter cortico-cortical connections with more lateralized parietal networks (Hari and Salmelin, 1997; Manshanden, De Munck, Simon, and da Silva, 2002), resulting in functional asymmetries showing a clear dominance of the right hemisphere.

Crucially, oscillatory activity in the alpha range (i.e., the IAF and the difference in the alpha power between the two hemispheres), showed a direct link with visuospatial performance across all participants. Participants performed the Grayscales task, a simple perceptual task testing visuospatial representation, in which healthy participants typically exhibit a leftward bias (Mattingley et al., 1994a; Mattingley et al., 2004), while patients with hemianopia show an ipsilesional bias (Tant et al., 2002b). The present results showed that the typical bias towards the visual hemifield contralateral to the intact/dominant hemisphere in the Grayscales task (Mattingley et al., 1994a; Mattingley et al., 2004; Tant et al., 2002b) was negatively correlated with the IAF (i.e., the lower the IAF, the higher the bias in the Grayscales task) and had a positive correlation with the interhemispheric imbalance in power (i.e., the higher the imbalance in power in favor of the intact hemisphere, the higher the perceptual bias). These findings corroborate the hypothesis that the oscillatory pattern in the alpha range at rest reflects behavioral visual performance and might represent an index of the efficiency of the visual system. Converging evidence have demonstrated that posterior alpha oscillations reflect the excitability of the visual cortices (Dugué et al., 2011; Romei et al., 2008a) and that prestimulus oscillatory activity in the alpha band can predict visual performance and

awareness (Benwell et al., 2019; Busch et al., 2009; Ergenoglu et al., 2004; Hanslmayr et al., 2007; Iemi and Busch, 2018; Limbach and Corballis, 2016; Samaha et al., 2017; Dijk et al., 2008). However, the functional role of alpha oscillations at rest has been less extensively investigated. The present findings strongly support the notion that oscillations in the alpha range at rest, measured by means of indices such as the IAF and the power, are intrinsic to the visual system and reflect its default organization (Hindriks et al., 2015) and functional efficiency. This interpretation is in line with recent evidence suggesting a direct link between the IAF and the cyclic sampling of visual information (Cecere et al., 2015; Samaha and Postle, 2015; Wutz, Muschter, van Koningsbruggen, Weisz, and Melcher, 2016; Wutz, Melcher, and Samaha, 2018) and an association between the amplitude of alpha oscillations and the efficiency of task execution (Klimesch, 1997; Klimesch, 1999; Mathewson et al., 2009).

In keeping, our results show that in hemianopic patients, also the performance in clinical visual tests had a strong association with the pattern of functioning in the alpha range. Indeed, visual detection performance in the blind field, when compensatory eye-movements were allowed (Bolognini et al., 2005), was positively correlated with IAF and showed a negative correlation with the imbalance in alpha power in favor of the intact hemisphere. On the contrary, no association between alpha parameters and visual performance when eye-movements were restricted was found. These findings suggest that alpha oscillatory activity after posterior lesions reflects visuospatial performance linked with spatial exploration and visual scanning behavior but is not associated to the size of the spared visual field. Yet, the visual detection task used in this study does not provide a fine grained measure of the visual field size (i.e., the stimuli are presented only at 8°, 24°,40° and 56°), therefore we cannot rule out the hypothesis that alterations in the activity in the alpha range might be linked also with visual detection abilities when eye-movements are not allowed. Thus, these findings show that the slowing down of alpha speed on the one hand and the strong interhemispheric imbalance in alpha activity after posterior lesions are suggestive of an overall impairment of the visual system which results detrimental for visual performance.

In contrast with the oscillatory patterns in the alpha range, we did not find any difference in left- and right-lesioned hemianopic patients concerning the degree of altered behavioral performance, in keeping with previous findings showing similar visuospatial bias in the Grayscales tasks (Tant et al., 2002b) and performance in visual detection (Passamonti et al. ,

2009) between hemianopic patients with left and right lesions. It is likely that the behavioral tasks used in the current study may not be sensitive enough to detect behavioral differences underpinned by different physiological indices.

Notably, post-lesional changes were also observed in the theta range, represented by an increase of the amplitude in this frequency band over the lesioned hemisphere. However, these alterations were less consistent and, more importantly, were not linked to a specific lesion profile. Indeed, the increase of theta power was found at the site of the lesion both in patients with posterior and anterior lesions. This finding is consistent with previous observations on patients with stroke, showing increased low frequency (delta/theta) oscillatory activity (Butz et al., 2004; Chu et al., 2015; Dubovik et al., 2012; Laaksonen et al., 2013; Tecchio et al., 2005). In contrast with the changes in the alpha range that are specific to posterior brain lesions and show a direct link with visual behavioral performance, the perilesional increase of low-frequency activity has been suggested to represent a lesion-induced signal for anatomical reorganization within the adult brain (Carmichael and Chesselet, 2002; Rabiller, He, Nishijima, Wong, and Liu, 2015), occurring regardless of the lesion site.

Chapter 3: Posterior lesions induce changes in Alpha functional connectivity reflecting visual performance

3.1. Introduction

Cognitive functioning is a distributed and dynamic process, requiring functional interactions between multiple brain regions and, thus, involving specific interplay among neural populations widely distributed in cortical and subcortical networks. Such interactions between both local and remote brain regions have been effectively studied by functional neural connectivity, an electrophysiological marker measuring the statistical interdependencies between EEG rhythms in a condition of resting-state, between different pairs of electrodes (Stam, Hillebrand, Wang, and Mieghem, 2010; Aertsen, Gerstein, Habib, and Palm. 1989). This electrophysiological functional coupling is able to capture relationship among different brain regions, which are essential for brain functioning (Tononi and Edelman, 1998; Varela, Lachaux, Rodriguez, and Martinerie, 2001).

Studies on the healthy brain have shown that EEG spontaneous fluctuations in the resting brain are typically highly organized and coherent (Greicius, Krasnow, Reiss, and Menon, 2003). However, a variety of neurological (Rossini, Rossi, Babiloni, and Polich, 2007; Babiloni et al., 2008; Babiloni, Lizio, Marzano, Capotosto, Soricelli, Triggiani, Cordone, Gesualdo, and Del Percio, 2016) and psychiatric (Fingelkurts, Fingelkurts, Rytsälä, Suominen, Isometsä, and Kähkönen, 2007; Haig, Gordon, De Pascalis, Meares, Bahramali, and Harris, 2000; Dawson, 2004) conditions have been shown to alter the typical pattern of functional connectivity, suggesting that these indices might represent a reflection of neural integrity. In line, brain lesions have shown to induce changes in functional connectivity in different frequency bands. More specifically, an increase in the number (Castellanos, Paúl, Ordóñez, Demuynck, Bajo, Campo, Bilbao, Ortiz, del-Pozo, and Maestú, 2010) and the functionality (Castellanos et al., 2010; Dubovik et al., 2012) of the connections in the in low frequency bands (delta/theta) have been described in patients with acquired brain lesions, compared to controls. In contrast, in the alpha range, a post-lesional reduction of brain connectivity has been reported, especially in intrahemispheric connections in the ipsilesional hemisphere (Dubovik et al., 2012; Westlake et al., 2012; Castellanos et al., 2010; Wu et al., 2011) and in interhemispheric interactions (Wu, Sun, Jin, Guo, Qiu, Zhu, and Tong, 2011).

However, also evidence of increased alpha connectivity has been provided in the contralesional hemisphere (Westlake et al., 2012) or in the intact regions of the lesioned hemisphere (Guggisberg, Honma, Findlay, Dalal, Kirsch, Berger, and Nagarajan, 2008; Wu et al., 2011). In addition, previous investigations have reported the presence of newly formed connections in the alpha range, both ipsilesional-to-contralesional and interhemispheric, in hemianopic patients with right lesions at the acute stage (i.e., within 3 months since onset; Guo, Jin, Feng, and Tong, 2014), but not in left-lesioned hemianopic patients (Wang, Guo, Sun, Jin, and Tong, 2012). Overall, similarly to the related studies on alpha parameters reported in the previous chapter, although alterations of the electrophysiological functionality of brain networks after brain lesions has been widely investigated, the results reported so far seems not fully consistent due to the variety of patients' clinical and lesion profiles. In line, it is unclear whether specific lesion profiles might be selectively associated with alterations in functional connectivity in different frequency bands during resting-state.

As extensively discussed in the previous chapters, the prominent oscillatory activity in the alpha range (7-13 Hz) observed during resting-state is mainly distributed over occipito-parietal regions (Rosanova et al., 2009). In addition, activity in the alpha range has been reported to be linked to the excitability of the visual cortices (Romei et al., 2008a) and to be associated to visual processing (Pfurtscheller et al., 1994) and visuospatial attention (Capilla et al., 2014). In this perspective, oscillations in the alpha range have been suggested to reflect, even at rest, the activity of the underlying neural populations (Klimesch et al., 2007; Sadaghiani and Kleinschmidt, 2016) and, thus, the functionality of the visual system. In line with this notion, it can be hypothesized that lesions to posterior cortices, which have been proposed to have a pivotal role in generating alpha oscillations (Thut et al., 2011; Bollimunta et al., 2008), might specifically alter oscillatory patterns and functional connectivity in the alpha range.

Accordingly, evidence provided so far in the chapter 2 has shown that posterior brain lesions in hemianopic patients can selectively reduce the alpha peak and power, while lesions to anterior regions do not alter alpha oscillatory patterns (Pietrelli, Zanon, Làdavas, Grasso, Romei, and Bertini, 2019). Interestingly, hemianopic patients with right lesions showed a more severe impairments of the oscillatory activity in the alpha range, with a more widely distributed reduction of IAF and a stronger interhemispheric imbalance in alpha power,

compared to hemianopic patients with left lesions, suggesting a functional asymmetry between the two hemispheres with a dominance of the right hemisphere in balancing interhemispheric inhibition (Pietrelli et al., 2019; Heilman and Van Den Abell, 1980; Kinsbourne, 1977). However, it is unclear whether hemianopic patients could show similar selective alterations also in functional connectivity in the alpha range. To test this hypothesis, EEG activity during eyes-closed resting-state was recorded in patients with left or right lesions to the posterior cortices, in control patients with left or right more anterior lesions and in a group of healthy controls. In addition, in line with previous findings suggesting a link between visual performance and altered alpha parameters in hemianopic patients (Pietrelli et al., 2019), visuospatial performance was measured with the Greyscales tasks (Mattingley et al., 1994a; Mattingley et al., 2004), to test whether connectivity in the alpha range might be predictive of the functioning of the visual system.

3.2. Methods

3.2.1. Participants

The study included 5 groups of participants. Two groups included patients with visual field defect due to lesions to the left (n = 12, 8 males, mean age = 51.4 years, mean time since lesion onset = 12.7 months) and right (n = 12, 9 males, mean age = 58.0 years, mean time since lesion onset = 13.3 months) posterior cortices. Right-lesioned patients were screened using the Behavioral Inattention Test neglect assessment (Wilson et al., 1987) to ensure performance was in the normal range. Two control groups included neurological patients with left (n = 7, 3 males, mean age = 43.9 years, mean time since lesion onset = 22.0 months) and right (n = 8, 4 males, mean age = 52.2 years, mean time since lesion onset = 23.6 months) anterior lesions without hemianopia. Finally, a control group included aged-matched participants without any neurological deficit (n = 16, 7 males, mean age = 54.1 years). No differences between the groups were found relative to age ($F_{4,50}$ = 1.48; p = 0.222) or time since lesion onset ($F_{3,35}$ = 1.02, p = 0.397). Clinical details are reported in Table 2.

ID	Sex	Age	Onset	Lesion site	Visual Field Defect	Aetiology
EMI01	M	81	9	Left Occipito-Temporal	Right hemianopia	Ischaemic
EMI02	M	69	5	Left Occipital	Right hemianopia	Ischaemic
EMI03	M	41	2	Left Occipital	Lower right quadrantopia	Ischaemic
EMI04	M	45	42	Left Fronto-Parieto-Temporal	Right hemianopia	Hemorragic

EMI05	M	51	5	Left Fronto-Temporo-Occipital	Right hemianopia	Abscess
EMI06	F	59	11	Left Temporal	Right hemianopia	AVM
EMI07	M	58	6	Left Temporo-Occipital	Right hemianopia	Ischaemic
EMI08	M	45	7	Left Temporal	Right hemianopia	Hemorragic
EMI09	F	57	28	Left Fronto-Temporo-Insular	Right hemianopia	AVM
EMI10	M	50	7	Left Temporo-Occipito-Parietal	Upper right quadrantopia	Ischaemic
EMI11	F	29	26	Left Temporal	Upper right quadrantopia	AVM
EMI12	F	32	4	Left Parieto-Occipital	Right hemianopia	Ischaemic
EMI13	M	56	3	Right Occipital	Left hemianopia	Ischaemic
EMI14	F	38	13	Right Parieto-Occipital	Left hemianopia	Hemorragic
EMI15	F	37	4	Right Occipito-Temporo-Parietal	Left hemianopia	Tumor
EMI16	M	58	18	Right Temporo-Occipital	Left hemianopia	Ischaemic
EMI17	F	73	8	Right Temporo-Occipital	Left hemianopia	Ischaemic
EMI18	M	81	7	Right Occipital	Left hemianopia	Hemorragic
EMI19	M	51	4	Right Occipital	Left hemianopia	Tumor
EMI20	M	60	29	Right Temporo-Occipital	Left hemianopia	Ischaemic
EMI21	M	77	6	Right Fronto-Parietal	Left hemianopia	Hemorragic
EMI22	M	30	54	Right Temporal	Left hemianopia	Hemorragic
EMI23	M	76	7	Right Occipital	Left hemianopia	Abscess
EMI24	M	59	6	Right Temporo-Occipital	Left hemianopia	Ischaemic
CON01	M	62	7	Left Temporo-Insular	No hemianopsia	Abscess
CON02	M	28	11	Left Fronto-Parietal	No hemianopsia	Tumor
CON03	F	45	39	Left Frontal	No hemianopsia	Tumor
CON04	F	46	12	Left Temporal Pole	No hemianopsia	Hemorragic
CON05	F	48	38	Left Fronto-Insular	No hemianopsia	Ischaemic
CON06	F	44	40	Left Frontal	No hemianopsia	Tumor
CON07	M	34	7	Left Frontal	No hemianopsia	Tumor
CON08	M	42	59	Right Frontal	No hemianopsia	Abscess
CON09	F	57	5	Right Fronto-Insular	No hemianopsia	AVM
CON10	F	42	19	Right Frontal	No hemianopsia	Tumor
CON11	M	51	3	Right Temporo-Insular	No hemianopsia	Tumor
CON12	F	51	5	Right Temporal	No hemianopsia	Tumor
CON13	M	52	6	Right Frontal	No hemianopsia	Tumor
CON14	M	75	22	Right Temporo-Insular	No hemianopsia	Tumor
CON15	F	50	70	Right Temporo-Fontro-Polar	No hemianopsia	TBI

Table 2. Summary of clinical data of all patients that took part to the study. Legend: M = Male; F = Female; AVM = Arteriovenous Malformation; TBI = Traumatic Brain Injury

Mapping of brain lesions was performed using MRIcro. Lesion documented by the most recent clinical CT or MRI were traced onto the T1-weighted MRI template from the Montreal Neurological Institute with MRIcro software (Rorden et al., 2007; Rorden and Brett, 2000) with the exception of EMI3, EMI17 and CONTROL13, whose MRI scans were not available. Lesions volumes were computed for each patient and the extent of the lesions were compared between the four patients' groups with a one-way ANOVA, revealing no significant

differences between groups ($F_{3,32} = 1.51$, $p = 0.232$). All patients showed normal or corrected-to-normal visual acuity. Patients were informed about the procedure and the purpose of the study and gave written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Regional Health Service Romagna (CEROM; n.2300).

3.2.2. Experimental design

All the participants completed the Grayscales Task (see below), then underwent an EEG recording session during eyes-closed resting-state. In order to probe the significance of the observed electrophysiological pattern for the visuospatial abilities of participants, a correlation between behavioral performance and electrophysiological activity was verified.

3.2.3. Greyscales task

In the Greyscales task (Mattingley et al., 2004), each stimulus consists of a pair of horizontal rectangles, one immediately above the other, presented on an LCD monitor. Each rectangle (height = 20 mm) was presented either in a short (width = 120 mm) and a long version (width = 260 mm) and was shaded continuously from black at one end to white at the other end. For each stimulus pair, one rectangle was darker at the right end and the other was darker at the left end (i.e. the two rectangles were mirror images of one another). Both rectangles within a pair had the same width. The entire task consists of 40 grayscale stimuli. The stimulus length (long versus short) and orientation (left upper dark and right lower dark versus right upper dark and left lower dark) were evenly displayed. Stimulus presentation was pseudo-randomized.

Participants seated in a sound-controlled room in front of a 24'' LCD monitor (refresh rate: 60 Hz, 1920 x 1080 pixel resolution) at a viewing distance of 57 cm. Participants were asked to identify which of the two rectangles comprising each stimulus appeared darker overall by saying 'top' or 'bottom'. Participants were encouraged to examine the stimuli carefully, were permitted to respond without time constraints and were allowed to use eye-movements to explore the entire stimulus display. No feedback on accuracy was provided during testing. Responses to each stimulus were categorized as left-biased when the participant selected the left darker end or right-biased when the participant selected the right darker end. An asymmetry score was then calculated ((trials number – left choices)/trials number – 0.5)*2 to quantify the direction and magnitude of any perceptual bias. This score was derived by the

normalization of the number of left choices. Specifically, the perceptual bias score could vary between -1, indicating the maximum bias towards the left hemifield and +1, indicating the maximum bias to the right hemifield. A score of 0, would account for absence of bias in a particular direction.

3.2.4. Resting-state EEG recording

All participants underwent 5 blocks of 1-minute resting-state EEG recording in a quiet room. They were asked to close their eyes and remain awake, while EEG signals were recorded with a BrainAmp DC amplifier (BrainProducts GmbH, Germany) and 59 Ag/AgCl electrodes mounted on an elastic cap (Fast'nEasy Cap, EasyCap GmbH, Germany) according the standard 10-20 coordinate system (Fp1, AF3, AF7, F1, F3, F7, FC1, FC3, FC5, FT7, C1, C3, C5, T7, CP1, CP3, CP5, TP7, P1, P3, P5, P7, PO3, PO7, O1, Fp2, AF4, AF8, F2, F4, F8, FC2, FC4, FC6, FT8, C2, C4, C6, T8, CP2, CP4, CP6, TP8, P2, P4, P6, P8, PO4, PO8, O2, FPz, AFz, Fz, FCz, Cz, CPz, Pz, POz, and Oz). Four external electrodes were used to monitor eye-movements. Specifically, two electrodes were placed on the outer canthi of both eyes to record horizontal movements, whereas two electrodes placed respectively beneath and above the left eye was used to monitor vertical movements and blinks. Reference and ground electrodes were placed on the left mastoid and the right cheek, respectively. The impedance was kept below 10 kΩ at all electrodes and the recorded signal was band-pass filtered at 0.01-100 Hz, digitized at a sampling rate of 1000 Hz and stored on a computer for subsequent off-line analyses.

3.2.5. EEG preprocessing

EEG recordings were processed off-line using EEGlab (EEGlab version 14.1.2; Delorme and Makeig, 2004) and custom routines developed in Matlab (R2018a, The Mathworks Inc., USA). Data from all electrodes were re-referenced to the average of all scalp electrodes and filtered with a band-pass filter of 1-100 Hz. Continuous signals were segmented in epochs of 1 seconds. Horizontal and vertical eye artifacts have been visually identified and corrected, after data dimension reduction by means of Principal Component Analysis (PCA). Data was down-sampled to 250 Hz and current source density (CSD) interpolation using spherical splines (Kayser and Tenke, 2015) was used to minimize confounding effects in inter-electrode synchronization due to volume conduction and electrical field spread (Cohen, 2014; van Diessen, Numan, van Dellen, van der Kooi, Boersma, Hofman, van Lutterveld, 2015). CSD

transformation was performed in Matlab using the open-source CSD toolbox (version 1.1; http://psychophysiology.cpmc.columbia.edu/). Time-frequency decomposition was performed for all EEG channels by using a multitaper method with digital prolate spheroidal sequence (DPSS) windows, implemented in Fieldtrip toolbox for EEG/MEG-analysis (Oostenveld, Fries, Maris, and Schoffelen, 2011). Complex Fourier coefficients were computed for the frequency band of interest (i.e., alpha band, 7-13 Hz) and for a control frequency band (theta band, 3-6 Hz). Finally, the weighted phase-lag index (wPLI; Vinck, Oostenveld, van Wingerden, Battaglia, and Pennartz, 2011) was computed for all possible pairs of electrodes and construct a 59x59 connectivity matrix for each participant and frequency band (i.e., alpha and theta). The wPLI is based on a consistent lag between the instantaneous phases of two electrodes and is less sensitive to zero-lag phase-relations typical for common sources (Bastos and Schoffelen, 2016; Hardmeier, Hatz, Bousleiman, Schindler, Stam, and Fuhr, 2014). The wPLI extends the PLI by weighting the contribution of observed phase leads and lags by the magnitude of the imaginary component of the cross-spectrum (Vinck et al., 2011).

3.2.6. Functional connectivity analysis

Since no standard procedures are currently available to assess similarities and differences in functional connectivity among groups and/or hemispheres (van Diessen et al., 2015), a multi-step approach was used to investigate, separately for each frequency band, the effect of the posterior brain lesion on functional connectivity and resting-state network topology.

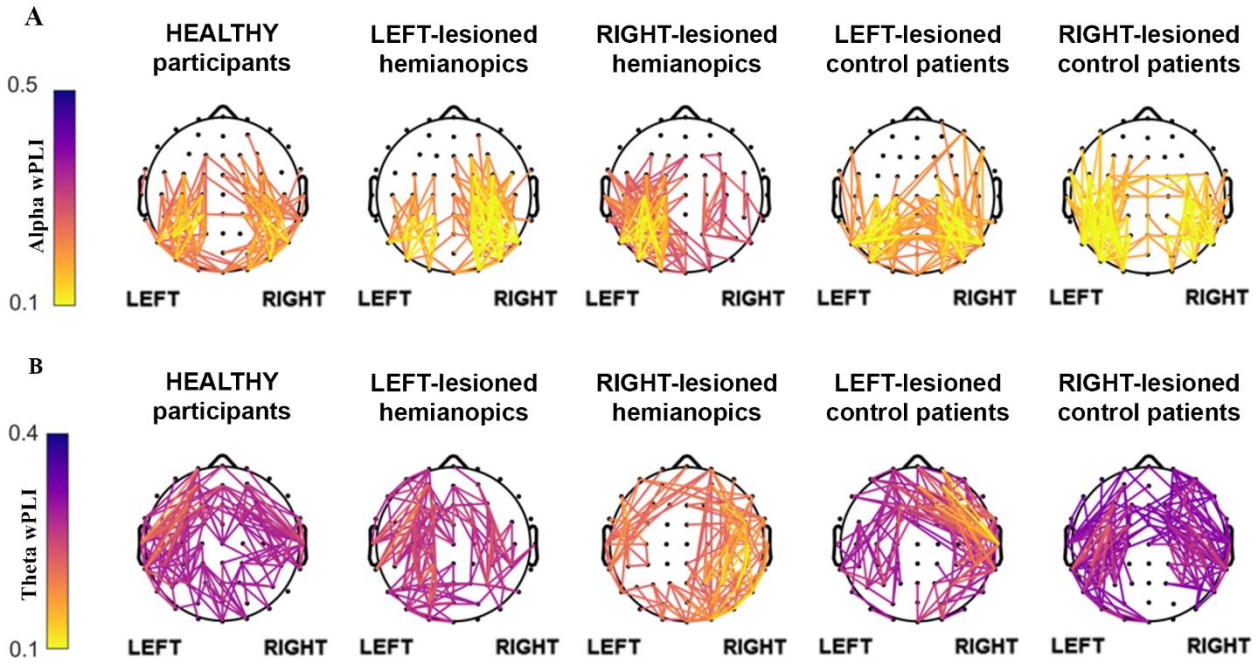

Figure 9. (A) The strongest Alpha connections (n = 171, 10% of total connections) in the five groups; (A) The strongest Theta connections (n = 171, 10% of total connections) in the five groups

To test for differences in functional connectivity, wPLI were averaged across electrodes separately for each participant and 4 scalp regions (see Figure 10-11, left anterior [LA]: Fp1, AF3, AF7, F1, F3, F7, FC1, FC3, FC5, and FT7; right anterior [RA]: Fp2, AF4, AF8, F2, F4, F8, FC2, FC4, FC6, FT8; left posterior [LP]: CP1, CP3, CP5, TP7, P1, P3, P5, P7, PO3, PO7, and O1; right posterior [RP]: CP2, CP4, CP6, TP8, P2, P4, P6, P8, PO4, PO8, and O2). Differences among groups and scalp regions were assessed separately for each frequency band (i.e., alpha and theta) by means of a repeated-measures ANOVA with *Group* (left-lesioned hemianopic patients, right-lesioned hemianopic patients, left-lesioned control patients, right-lesioned control patients, healthy participants) as between-subjects factor and *Hemisphere* (Left, and Right) and *Region* (Anterior, and Posterior) as within-subjects factors. Post-hoc comparisons were carried out using Duncan tests. Significance level was set at $p = 0.05$. To assess the behavioral and clinical significance of changes in functional connectivity patters in the alpha and theta band, mean wPLI were correlates with Greyscales Task score for all participants. Pearson's r and the relative p-value was computed for each correlation. Significance level was set at $p = 0.05$.

3.3. Results

3.3.1. Alpha wPLI

The overall ANOVA for the Alpha wPLI revealed a significant *Group* x *Hemisphere* x *Region* interaction ($F_{4,50} = 5.32$, $p = 0.001$). To explore this interaction, two ANOVAs on Alpha wPLI values with *Hemisphere* (left hemisphere, right hemisphere) and *Group* (left-lesioned hemianopic patients, right-lesioned hemianopic patients, left-lesioned control patients, right-lesioned control patients, healthy participants) as factors were run separately for the *posterior* and the *anterior* regions (see Fig 10).

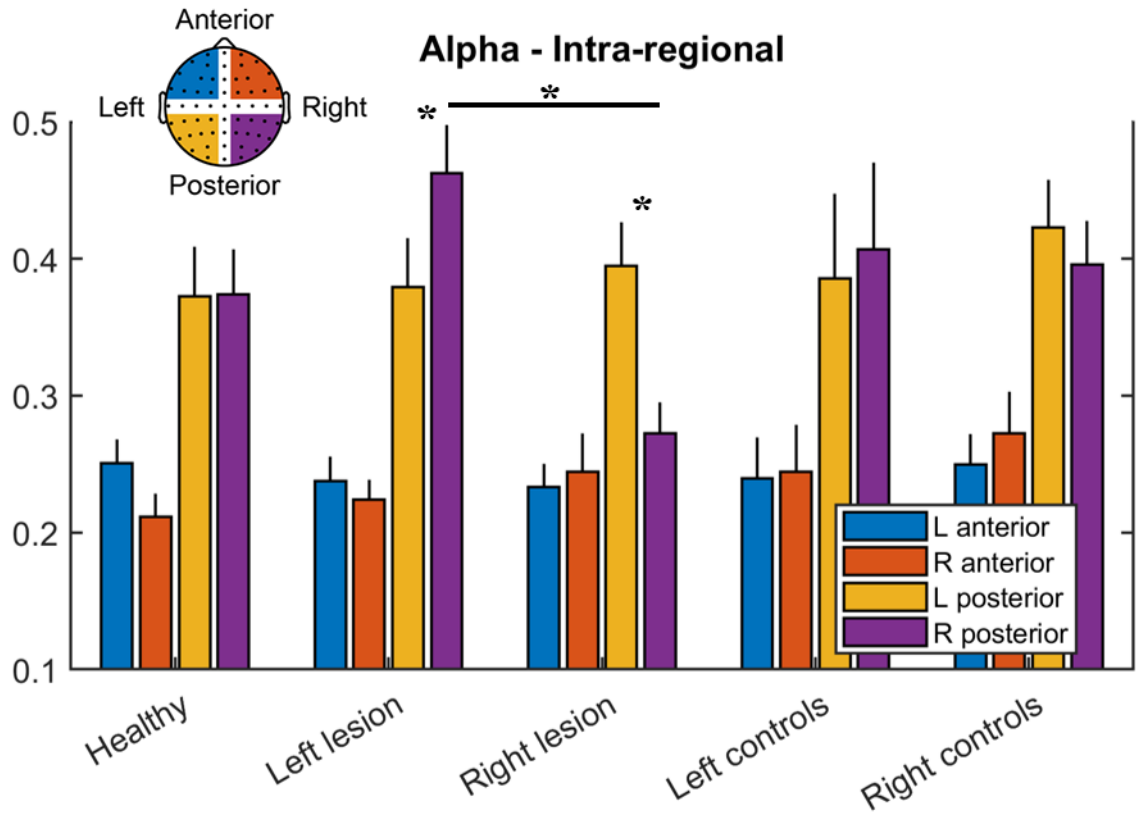

Figure10. Scalp topography on the top left represents the scalp distribution of the four ROIs investigated. Bar plots show mean Alpha wPLI values in the posterior and anterior regions of the left and right hemisphere of the five experimental groups. Error bars represent SEM. Asterisks denote significant comparisons

The ANOVA for the *posterior* region showed a significant *Hemisphere* x *Group* interaction ($F_{4,50} = 6.16$, $p < 0.001$). More precisely, in left-lesioned hemianopic patients the right-intact hemisphere (M = 0.46) showed a greater Alpha wPLI compared to the left-lesioned hemisphere (M = 0.38, p = 0.030). Similarly, in right-lesioned hemianopic patients the left-intact hemisphere (M = 0.40) showed a higher Alpha wPLI compared to the right-lesioned

hemisphere (M = 0.27, p = 0.001). Furthermore, the Alpha wPLI was greater in the right-intact hemisphere of left-lesioned hemianopic patients compared to the right hemisphere of the right-lesioned hemianopic patients (p = 0.006). No other significant effects were found (all ps > 0.45). The ANOVA for the *anterior* region showed no significant main or interaction effects (all ps > 0.41). Summarizing, these results suggest that Alpha functional connectivity is reduced in the lesioned hemisphere after both left and right posterior brain lesions.

To further investigate the alpha functional connectivity pattern within the posterior ROIs, we also compared the Alpha wPLI of each electrode in posterior ROIs of hemianopic and control patients with healthy participants. To this aim, pairwise comparisons, using unpaired-samples *t*-tests, were conducted for each pair of posterior electrodes between healthy participants and both left- and right-lesioned hemianopic patients. Significance level was set at p = 0.01.
The unpaired-samples *t*-tests on Alpha wPLI in posterior ROIs comparing left-lesioned hemianopic patients and healthy participants showed significant differences for several electrodes pairs in the right hemisphere (CP2-P2, P2-O2, P2-P8, P2-PO8, P2-PO4, CP2-PO4, CP2-PO8 and P4-P6). Specifically, in each significant electrodes pair of the right hemisphere, the Alpha wPLI was greater in the left-lesioned hemianopic patients compared to healthy participants.

Similarly, the unpaired-samples *t*-tests on Alpha wPLI in posterior ROIs comparing right-lesioned hemianopic patients and healthy participants showed significant differences for several electrodes pairs in the right hemisphere (O2-P8, O2-TP8, O2-P6, O2-CP6, PO8-P8, PO8-P6, PO8-CP6, PO4-P4, PO4-P6 and P6-TP8). However, contrary to left-lesioned hemianopic patients, in each significant electrodes pair of the right hemisphere, the Alpha wPLI was reduced in the right-lesioned hemianopic patients compared to healthy participants.

The unpaired-samples *t*-tests on Alpha wPLI in posterior ROIs comparing left-lesioned control patients and healthy participants showed only one significant difference in the electrodes pair CP5-PO3 in the left hemisphere, and another in the electrodes pair TP8-P8 in the right hemisphere. Specifically, in both the right and left hemisphere electrodes pair found, the Alpha wPLI was lower in the left-lesioned control patients compared to healthy participants. Moreover, the unpaired-samples *t*-tests on Alpha wPLI in posterior ROIs between right-lesioned control patients and healthy participants showed no significant

differences between each electrode's pairs in both the right-lesioned and left-intact hemisphere.

3.3.2. Theta wPLI

The overall ANOVA for the Theta wPLI revealed a significant *Group* main effect ($F_{4,50}$ = 5.46, $p < 0.001$; see Fig 11). More precisely, the right-lesioned hemianopic patients showed a greater Theta wPLI (M = 0.25) compared to all other groups (healthy participants M = 0.17, p = 0.004; left-lesioned hemianopic patients M = 0.19, p = 0.011; left-lesioned control patients M = 0.18, p = 0.005; right-lesioned control patients M = 0.15, $p < 0.001$). Furthermore, a significant *Hemisphere* x *Group* interaction ($F_{4,50}$ = 3.61, p = 0.012) was found. Specifically, in right-lesioned hemianopic patients the right-lesioned hemisphere (M = 0.27) showed a greater Theta wPLI compared to the left-intact hemisphere (M = 0.23, p = 0.028). More importantly, the right-lesioned hemisphere of right-lesioned hemianopic patients showed also a greater Theta wPLI compared to both left and right hemisphere of all the other groups (all ps < 0.018). In addition, also the left-intact hemisphere in the right-lesioned hemianopic patients showed higher Theta wPLI, compared to the left-intact hemisphere (p = 0.002) of right-lesioned control patients and trends towards higher Theta wPLI compared to the left hemisphere of healthy participants (p = 0.073) and both the left-lesioned (p = 0.057) and right-intact (p = 0.068) hemispheres of left-lesioned control patients. No other significant main or interaction effects were found (all ps > 0.160). Summarizing, results suggest that the Theta functional connectivity increases after a right posterior lesion, more strongly in the right-lesioned compared to the left-intact hemisphere.

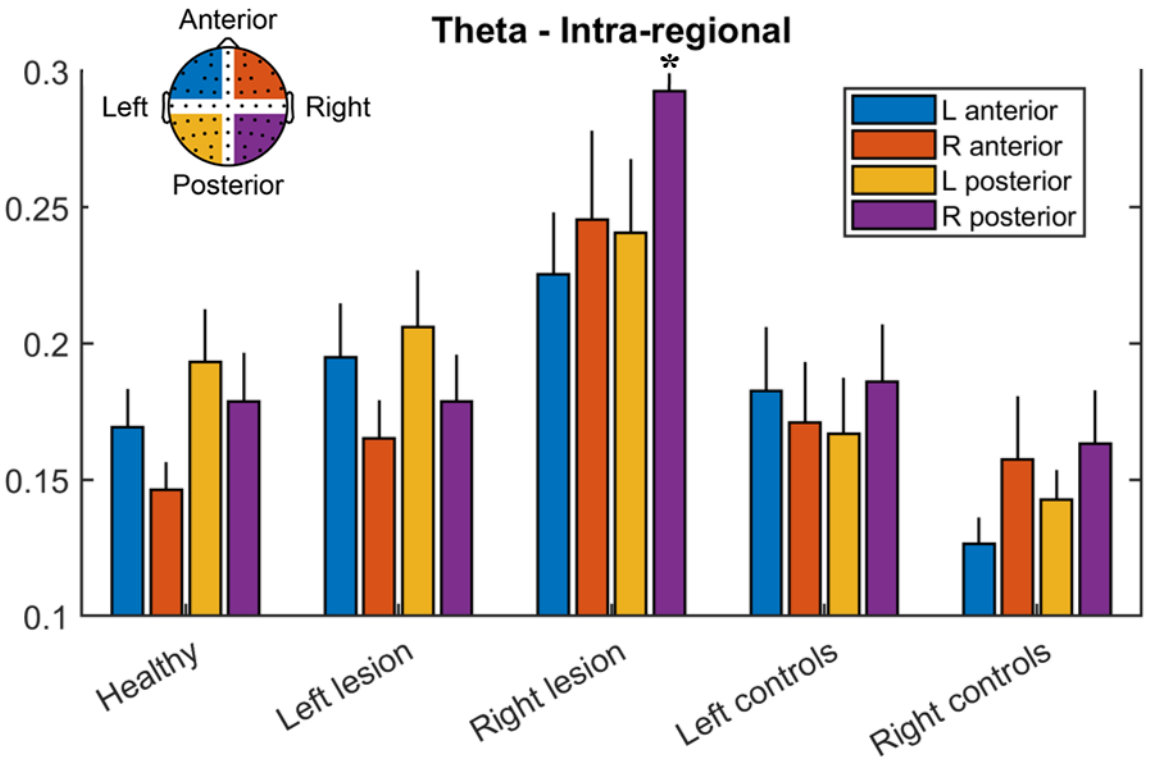

Figure11. Scalp topography on the top left represents the scalp distribution of the four ROIs investigated. Bar plots show mean Theta wPLI values in the posterior and anterior regions of the left and right hemisphere of the five experimental groups. Error bars represent SEM. Asterisks denote significant comparisons

Similarly to the exploratory analysis on posterior ROIs Alpha wPLI, we also compared the Theta wPLI of each electrode in posterior ROIs of hemianopic and control patients with healthy participants. Therefore, a pairwise comparison, with unpaired-samples *t*-tests, was conducted for each pair of posterior electrodes comparing healthy participants and both left- and right-lesioned hemianopic and control patients. Significance level was set at p = 0.01.

The unpaired-samples *t*-tests on Theta wPLI in posterior ROIs between left-lesioned hemianopic patients and healthy participants showed no significant differences between each electrodes pairs in both the right-intact and left-lesioned hemisphere. In contrast, the unpaired-samples *t*-tests on Theta wPLI in posterior ROIs between right-lesioned hemianopic patients and healthy participants showed four significant pairs of electrodes in the right-lesioned hemisphere (CP6-P6, PO8-TP8, PO8-P8 and TP8-P8). Specifically, in each significant couple of electrodes in the right hemisphere the Theta wPLI was higher in the right-lesioned hemianopic patients compared to healthy participants.

The unpaired-samples *t*-tests on Theta wPLI in posterior ROIs comparing left-lesioned control patients and healthy participants showed only one significant difference in the electrodes pair P5-PO7 in the left hemisphere. Specifically, the Theta wPLI was lower in the left-lesioned control patients compared to healthy participants. Similarly, the unpaired-samples *t*-tests on Theta wPLI in posterior ROIs between right-lesioned control patients and healthy participants showed only one significant difference in the electrodes pair P1-TP7 in the left hemisphere. Specifically, the Theta wPLI was lower in the right-lesioned control patients compared to healthy participants.

3.3.3. Greyscales Task

Next, we looked at whether posterior Alpha wPLI could account for visual performance. First, we explored behavioral differences between groups in the Greyscales task. The one-way ANOVA on the Greyscales Task score showed a significant main effect of *Group* ($F_{4,50}$ = 11.56, $p < 0.001$). The post-hoc analysis showed a significantly greater Grayscales Task score in right-lesioned hemianopic patients (M = 0.64) compared to all the other groups (healthy participants M = -0.14, $p < 0.001$; left-lesioned hemianopic patients M = -0.54, $p < 0.001$; left-lesioned control patients M = -0.32, p = 0.002; right-lesioned control patients M = 0.21, p = 0.004).

Further, we investigated whether there was a relationship between the participant's visuospatial bias and Alpha and Theta wPLI, which resulted altered in previous analysis. Specifically, Greyscales task bias score was correlated with Alpha wPLI within the posterior regions of the right hemisphere and Theta wPLI of both the right and left hemisphere. The results showed a negative correlation between right posterior Alpha wPLI and the Greyscales task bias score (R_{55} = -0.50, $p < 0.001$), i.e. the lower the right posterior Alpha wPLI the higher the bias towards the right visual field, whereas the higher the right posterior Alpha wPLI the higher the bias towards the left visual field. Concerning the results in the theta band, a positive correlation was found between right posterior Theta wPLI and the Greyscales task bias score (R_{55} = 0.45, p = 0.001), i.e. the lower the right Theta wPLI the higher the bias towards the left visual field, whereas the higher the right Theta wPLI the higher the bias towards the right visual field.

3.4. Discussion

Hemianopic patients with posterior brain lesions show alterations in functional connectivity in the alpha range, while no significant alterations in alpha connectivity was found in control patients with more anterior lesions. Specifically, the present findings show that in the posterior regions of both hemianopic patients with left and right lesions the alpha connectivity was reduced in the lesioned hemisphere, compared to the intact hemisphere. Interestingly, this interhemispheric imbalance was mainly driven by the pattern of functional connectivity observed in the right hemisphere. Namely, in hemianopic patients with right lesions, functional connectivity in the right lesioned hemisphere showed a significant reduction compared to controls, while the left intact hemisphere does not show differences compared to controls. In contrast, in hemianopic patients with left lesions, the right intact hemisphere showed a significant increase in alpha connectivity, while no difference was found in the left lesioned hemisphere, compared to controls. In other words, lesions to the posterior cortices selectively induced changes in alpha connectivity, both in hemianopic patients with right and left hemispheric lesions. However, opposite patterns of functional connectivity were found in the right hemisphere between the two groups, which showed reduced connectivity when lesioned (i.e., in hemianopic patients with right lesions) and increased connectivity when intact (i.e., in hemianopic patients with left lesions). No difference in functional connectivity was found in the left hemisphere of hemianopic patients with left or right lesions, compared to controls.

Alpha oscillations (7-13 Hz) are the dominant frequency range of activity of the resting human brain and their distribution is prominent over posterior cerebral regions (Rosanova et al., 2009; Berger, 1929). Accordingly, posterior visual cortices have been demonstrated to be crucial in generating and propagating alpha oscillations in the visual system (Bollimunta et al., 2008; Hindriks et al., 2015). In addition, oscillations in the alpha range are linked to visual perception and visual cortex activity (Pfurtscheller et al., 1994; Romei et al., 2008a). This is in line with the present findings showing that lesions to posterior brain regions might alter alpha oscillatory patterns, reflecting the underlying functioning of the visual system. Previous evidence from the study in the chapter 2 has revealed the presence of a slowdown of the speed of processing in the alpha range and a reduction of alpha power in patients with hemianopia and posterior lesions (Pietrelli et al., 2019). Similarly, the present findings reveal that

posterior lesions reduce the functional connectivity in the alpha range. Long-range alpha synchronous activity has been shown to be relevant to promote communication between regions according to task demands (Palva and Palva, 2007; Doesburg, Green, McDonald, and Ward, 2009). In addition, alpha cortico-cortical interactions have been suggested to reflect top-down processing, subserving the ability to integrate local, bottom-up information (Stein and Sarnthein, 2000). Thus, functional connectivity in the alpha range during rest can represent an index of the structural and functional integrity of the visual system. Accordingly, converging evidence has shown impaired pattern of alpha functional connectivity in patients with visual loss due to pre-chiasmatic lesions (Bola, Gall, Moewes, Fedorov, Hinrichs, and Sabel, 2014) or retinal damage (Bola, Gall, and Sabel, 2015).

Interestingly, the right hemisphere demonstrates different patterns of post-lesional changes in alpha connectivity, depending on the lateralization of the lesion. Namely, the alpha functional connectivity in the right hemisphere showed a reduction when the hemisphere is lesioned and an increase, when the hemisphere is spared (i.e., in the presence of lesions to left hemisphere). This suggests that posterior lesions to the right hemisphere have a more detrimental effect on the functional interactions in the alpha range. However, when posterior lesions involve the left hemisphere, the right intact hemisphere reveals an enhanced alpha functional connectivity, which can possibly represent a post-lesional compensatory mechanism. This seems to suggest a prominent role of the right hemisphere in distributing spontaneous alpha activity and in organizing alpha network interactions. Taking into account the functional role of alpha oscillatory activity in visual and visuospatial attentional performance (Romei et al., 2008a; Capilla et al., 2014), these findings seem in line with the well-known dominance of the right hemisphere in spatial representation (Heilman and Van Den Abell, 1980) and in balancing interhemispheric activity (Kinsbourne, 1977).

Notably, right hemisphere alpha functional connectivity was associated with behavioral performance in visuospatial tasks. Visuospatial performance was tested with the Greyscales task (Mattingley et al., 1994a; Mattingley et al., 2004), a simple perceptual task in which healthy participants typically show a leftward bias, while hemianopic patients exhibit an ipsilesional bias (Pietrelli et al., 2019; Tant et al., 2002b). The results showed a negative association between alpha functional connectivity in the right hemisphere and the bias towards the right hemifield, i.e. the higher the right posterior connectivity the higher the bias

toward the left hemifield and the lower the right posterior connectivity the higher the bias toward the right hemifield. Therefore, the visuospatial bias toward the hemifield contralateral to the intact/dominant hemisphere, usually found in the literature, is entirely described by the alpha functional connectivity only in the right hemisphere, regardless to the side of the lesion. This is in line with previous findings showing a link between perceptual bias in hemianopic patients and oscillatory alpha activity (i.e., IAF and alpha power; Pietrelli et al., 2019) and corroborate the hypothesis that alpha pattern at rest might reflect an index of the efficiency of the visual processing.

Interestingly, although previous reports have documented post-lesional increased connectivity in low frequencies (delta-theta; Castellanos et al., 2010; Dubovik et al., 2012), the present findings do not show systematic alterations in the connectivity in theta range in patients with posterior or anterior lesions. More precisely, only patients with posterior lesions to the right hemisphere showed enhanced functional connectivity in the theta range, in the right lesioned hemisphere. We can speculate that this finding might represent a compensatory mechanism for the loss of alpha functional connectivity after right posterior lesions. Accordingly, observations on neurological patients with thalamic dysfunctions have shown that, when activity in the alpha range is absent, typical alpha functional changes (i.e., desynchronization upon opening of the eyes) can, in turn, be shifted to theta frequency (Sarnthein, Morel, von Stein, and Jeanmonod, 2005). However, a significant correlation between functional connectivity in the theta range in the right hemisphere and visual performance has been observed in the current findings, thus suggesting that the theta oscillatory alteration observed in right-lesioned hemianopic patients might reflect a possible additional dysfunction in the connectivity pattern.

In this perspective, it can be argued that hemianopic patients with right lesions report a more pervasive alteration in functional connectivity. Indeed, they show both reduced connectivity in the alpha range and increased connectivity in the theta range. Since alpha oscillatory activity has been proposed to reflect widespread cortical networks' activity, regulating focal processes in non-alpha frequency bands (Doesburg et al., 2009; Barry and Blasio, 2017), the altered connectivity pattern in hemianopic patients with right lesions suggests that a post-lesional reduction in alpha connectivity in the right hemisphere induce also impairments in local processes in lower-frequency bands. This strengthens the hypothesis of the role of alpha

oscillations in orchestrating oscillatory activity in different frequency bands (Hindriks et al., 2015) and suggest that the right hemisphere might have a pivotal role in this mechanism.

Overall, the present results suggest that functional connectivity in the alpha range can be altered after posterior lesions, indicating that this measure might represent the integrity of the underlying visual system. In addition, alterations in the alpha range in the right hemisphere might induce related dysfunctions also in lower frequency bands.

Chapter 4: Alterations in alpha reactivity in eyes-closed and eyes-open resting-state in hemianopic patients

4.1. Introduction

Alpha rhythm (7-13 Hz) is the dominant EEG pattern during eyes-closed resting condition in healthy awake individuals (Berger, 1929; Rosanova et al., 2009). Synchrony of alpha oscillations at rest has been traditionally linked to a sort of a standby state (Palva and Palva, 2007). This idea of alpha oscillations as the brain "idle rhythm" was supported by early observations of increased alpha power during relaxed wakefulness with eyes-closed (Bazanova and Vernon, 2014), as well as by studies that described a dominant alpha pattern during meditation (Travis and Wallace, 1999) and some states of coma (Ben-Simon, Podlipsky, Arieli, Zhdanov, and Hendler, 2008; Niedermeyer, 1997). However, more recent perspectives have proposed an association between alpha power and the tonic and distributed synchronous activity of the underlying neurons (Klimesch et al., 2007; Sadaghiani and Kleinschmidt, 2016). In keeping with this idea, alpha power during eyes-closed resting state, recorded over occipito-parietal electrodes, might index active suppression of neural predictions in the visual system (Sadaghiani and Kleinschmidt, 2016), reflecting an active engagement of the neurons of the underlying neural population.

A typical observation in studies on relaxed wakefulness with eyes-closed is the decrease of alpha amplitude at the opening the eyes (Barry, Clarke, Johnstone, Magee, and Rushby, 2007; Ben-Simon et al., 2008). The decrease of alpha amplitude induced by eyes opening, known as alpha desynchronization or alpha suppression (Berger, 1929) is a consistent effect observed prominently over the posterior areas of the brain (Ben-Simon, Podlipsky, Okon-singer, Gruberger, Cvetkovic, Intrator, and Hendler, 2013; Marx, Stephan, Nolte, Deutschländer, Seelos, Dieterich, and Brandt, 2003), but occurring all over the scalp without evident topographical changes (Barry et al., 2007; Barry and De Blasio, 2017). In addition to alpha suppression, the opening of the eyes also induces changes in non-alpha frequency bands, which, however, typically show a more focal distribution (Barry et al., 2007; Barry and De Blasio, 2017). The widespread alpha suppression at the opening of the eyes has been also reported to be positively correlated with increase in skin conductance levels, possibly reflecting large cortical arousal changes induced by merely opening the eyes (Barry et al., 2007). The complex of this global and local oscillatory changes at the opening of the eyes

might reflect increased visual system activity (Barry and De Blasio, 2017), which has been linked to widespread cortical and subcortical-cortical interactions (Klimesch, 1999; Başar, 1999). Accordingly, oscillatory reactivity to the opening of the eyes has been attributed to uncoupling of thalamo-cortical connections (Klimesch, 1999). However, functional connectivity in cholinergic pathways linking the basal nucleus of Meynert to visual cortex (Wan, Huang, Schwab, Tanner, Rajan, Lam, Zaborszky, Li, Price, and Ding, 2019) and ascending projections from the Reticular Activating System (Gale, Coles, and Boyd, 1971; Härdle, Gasser, and Bächer, 1984; Volavka, Matoušek, and Roubíček, 1967; Garcia-Rill, Kezunovic, Hyde, Simon, Beck, and Urbano, 2013) have been also proposed to have a role in alpha suppression in the transition from eyes-closed to eyes-open resting state.

EEG reactivity induced by eyes-opening is maintained across life-span in healthy participants but tends to be reduced with age (Barry et al., 2007; Barry, Clarke, Johnstone, and Brown, 2009; Barry and De Blasio, 2017). However, investigations on alpha reactivity on clinical populations are limited. Altered alpha reactivity induced by eyes-opening was found in dementia (van der Hiele, Bollen, Vein, Reijntjes, Westendorp, van Buchem, Middelkoop, and van Dijk, 2008) and schizophrenia (Colombo, Gambini, Macciardi, Bellodi, Sacchetti, Vita, Cattaneo, and Scarone, 1989), but little is known about how brain lesion impacts on EEG reactivity caused by eyes-opening.

The study presented in the chapter 2 (Pietrelli et al., 2019) on patients with posterior brain lesions and hemianopia, demonstrated that lesions of the posterior cortices result in a pathological alpha oscillatory pattern during eyes-closed resting-state, with a slowdown of the individual alpha frequency peak (IAF) and a reduction of the amplitude in the lesioned hemisphere, which was more pronounced in hemianopic patients with right lesions, compared to hemianopic patients with left lesions. In addition, evidence reported in the previous chapter also showed that connectivity in the alpha range is altered after posterior brain lesions. This observation suggests that alpha oscillations might reflect the functionality of the posterior cortices and represent an electrophysiological fingerprint of the functioning of the visual system. In line, a wide range of evidence converge on the notion that different alpha parameters are linked to visual and attentional processes (Ben-Simon et al., 2008; Pfurtscheller et al., 1994; Capilla et al., 2014).

The evidence showing that posterior lesions alter alpha oscillatory parameters (Pietrelli et al., 2019) raise the question whether the residual alpha recorded in hemianopic patients during eyes-closed resting-state can retain the typical reactivity to the opening of the eyes. More precisely, it can be hypothesized that damage to posterior cortices results in disrupted or altered alpha desynchronization in the transition from the eyes-closed to the eyes-open resting-state. To test this hypothesis, a group of hemianopic patients with posterior left lesions, a group of hemianopic patients with posterior right lesions, a control group of patients with more anterior lesions and a control group of healthy participants were tested, recording EEG during rest, both during eyes-closed and eyes-open conditions.

4.2. Methods

4.2.1. Participants

Four groups of participants took part to the study: one group of twelve patients with visual field defect due to lesions to the left posterior cortices (9 males, mean age = 52.3 years, mean time since lesion onset = 12.4 months), one group of twelve patients with visual field defect due to lesions to the right posterior cortices (9 males, mean age = 58 years, mean time since lesion onset = 13.3 months), a control group of twelve patients without hemianopia with fronto-temporal lesions sparing the posterior cortices (6 males, mean age = 48.2 years, mean time since lesion onset = 26 months), and a control group of twelve age-matched healthy participants (6 males, mean age = 58 years). No differences between the groups were found in terms of age ($F_{3,44} = 1.10$; $p = 0.363$) or time since lesion onset ($F_{2,33} = 2.41$; $p = 0.105$); (for clinical details, please see Table 3).

ID	Sex	Age	Onset	Lesion site	Visual Field Defect	Aetiology
HEMI01	M	69	5	Left Occipital	Right hemianopia	Ischaemic
HEMI02	M	45	7	Left Temporal	Right hemianopia	Hemorragic
HEMI03	F	57	28	Left Fronto-Temporo-Insular	Right hemianopia	AVM
HEMI04	M	50	7	Left Temporo-Occipito-Parietal	Upper right quadrantopia	Ischaemic
HEMI05	M	81	9	Left Occipito-Temporal	Right hemianopia	Ischaemic
HEMI06	M	51	5	Left Fronto-Temporo-Occipital	Right hemianopia	Abscess
HEMI07	M	41	2	Left Occipital	Lower right quadrantopia	Ischaemic
HEMI08	M	45	42	Left Fronto-Parieto-Temporal	Right hemianopia	Hemorragic
HEMI09	F	29	26	Left Temporal	Upper right quandrantopia	AVM
HEMI10	M	58	6	Left Temporo-Occipital	Right hemianopia	Ischaemic
HEMI11	F	32	4	Left Parieto-Occipital	Right hemianopia	Ischaemic

HEMI12	M	69	8	Left Temporo-Occipital	Right hemianopia	Hemorragic
HEMI13	M	56	3	Right Occipital	Left hemianopia	Ischaemic
HEMI14	F	38	13	Right Parieto-Occipital	Left hemianopia	Hemorragic
HEMI15	F	37	4	Right Occipito-Temporo-Parietal	Left hemianopia	Tumor
HEMI16	M	58	18	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI17	M	81	7	Right Occipital	Left hemianopia	Hemorragic
HEMI18	M	51	4	Right Occipital	Left hemianopia	Tumor
HEMI19	M	60	29	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI20	F	73	8	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI21	M	77	6	Right Fronto-Parietal	Left hemianopia	Hemorragic
HEMI22	M	30	54	Right Temporal	Left hemianopia	Hemorragic
HEMI23	M	59	6	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI24	M	76	7	Right Occipital	Left hemianopia	Abscess
CON01	F	48	38	Left Fronto-Insular	No hemianopia	Ischaemic
CON02	F	44	40	Left Frontal	No hemianopia	Tumor
CON03	M	28	11	Left Fronto-Parietal	No hemianopia	Tumor
CON04	F	45	39	Left Frontal	No hemianopia	Tumor
CON05	F	57	5	Right Fronto-Insular	No hemianopia	AVM
CON06	M	42	59	Right Frontal	No hemianopia	Abscess
CON07	M	62	7	Left Temporo-Insular	No hemianopia	Abscess
CON08	F	42	19	Right Frontal	No hemianopia	Tumor
CON09	M	34	7	Left Frontal	No hemianopia	Tumor
CON10	M	51	3	Right Temporo-Insular	No hemianopia	Tumor
CON11	F	50	70	Right Temporo-Fronto-Polar	No hemianopia	TBI
CON12	M	75	22	Right Temporo-Insular	No hemianopia	Tumor

Table 3. Summary of clinical data of all patients that took part to the study. Legend: M = Male; F = Female; AVM = Arteriovenous Malformation

Mapping of brain lesions was performed using MRIcro. Lesions documented by the most recent clinical CT or MRI were traced onto the T1-weighted MRI template from the Montreal Neurological Institute provided with MRIcro software (Rorden et al., 2007; Rorden and Brett, 2000), with the exception of HEMI8 and HEMI20 whose MRI scans were not available. Lesions volumes were computed for each patient and the extents of the lesions were compared between the three patients' groups, revealing no significant differences (one-way ANOVA, $F_{2,31} = 0.77$; $p = 0.472$) between hemianopic patients with left lesions, hemianopic patients with right lesions and control patients. In patients with right lesions the presence of neglect was screened using the Behavioral Inattention Test (Wilson et al., 1987), to ensure performance was in the normal range. All patients showed normal or corrected-to-normal visual acuity. Patients were informed about the procedure and the purpose of the study and gave written informed consent. The study was designed

and performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Regional Health Service Romagna (CEROM; n.2300).

4.2.2. Experimental design

Participants comfortably seated at rest in a sound-proof room in front of a 24'' LCD monitor (refresh rate 60 Hz) at a viewing distance of 57 cm. EEG signal was recorded in five sessions of one-minute for each of the two resting conditions: eyes-closed and eyes-open resting-state. During the eyes-open resting-state, participants were asked to fixate a white central fixation cross (0.5°) against a black background on the monitor. Each one-minute session of recording was alternated between the two resting conditions. EEG data was acquired through a BrainAmp DC amplifier (BrainProducts GmbH, Germany) and Ag/AgCl electrodes (Fast'nEasy Cap, Easycap GmbH, Germany) from 59 scalp sites (Fp1, AF3, AF7, F1, F3, F7, FC1, FC3, FC5, FT7, C1, C3, C5, T7, CP1, CP3, CP5, TP7, P1, P3, P5, P7, PO3, PO7, O1, Fp2, AF4, AF8, F2, F4, F8, FC2, FC4, FC6, FT8, C2, C4, C6, T8, CP2, CP4, CP6, TP8, P2, P4, P6, P8, PO4, PO8, O2, FPz, AFz, Fz, FCz, Cz, CPz, Pz, POz, Oz) and the right mastoid. The left mastoid was used as reference electrode, while the ground electrode was placed on the right cheek. Vertical and horizontal electrooculogram (EOG) components were recorded from above and below the left eye, and from the outer canthus of each eye. Data was recorded with a band-pass filter of 0.01–100 Hz and digitized at a sampling rate of 1000 Hz, while impendences were kept under 10 KΩ. Raw EEG signal was off-line pre-processed and analyzed with EEGLAB (EEGlab version 4.1.2b; Delorme and Makeig, 2004), using custom Matlab routines (R2017a; The Mathworks Inc., USA). Data from all electrodes were re-referenced to the average of all scalp electrodes and filtered with a band-pass filter of 1-100 Hz. The first 10 seconds of each one-minute recording session were excluded from the analysis, in order to avoid any contamination of the signal related to the transition from eyes-closed to the eyes-open resting condition. Continuous signal was segmented in epochs of 2 seconds. Data dimensionality was reduced to 32 components based on principal component analysis (PCA) and horizontal and vertical eye artifacts were visually identified and discarded. On the cleaned EEG signal, an FFT was computed on the 2-sec epochs, with a frequency resolution of 0.5 Hz. Then, the amplitude of alpha and theta oscillations was calculated as the average power (in dB) in each electrode between 7 and 13 Hz and 4 and 6

Hz, respectively. In order to compare the lesioned and intact hemispheres across participants, electrodes were swapped cross-hemispherically for patients with lesions to the right hemisphere (i.e., the data were analyzed as if all patients were left-lesioned).

Then, regions of interests (ROIs) were selected to perform statistical analysis on alpha and theta power. Specifically, the more anterior electrodes were excluded from the analysis, to avoid contamination of the signal by the ocular artifacts. Moreover, electrodes on the sagittal midline were also excluded to provide a better segregation of the signal between the two hemispheres. Thus, six right parieto-occipital electrodes (P4, P6, P8, PO4, PO8, O2) were selected to represent the posterior ROI of the intact/right hemisphere and the corresponding homologue electrodes (P3, P5, P7, PO3, PO7, O1) were selected to represent the posterior ROI of the lesioned/left hemisphere. In line, visual inspection of the scalp distribution of the mean alpha activity between 7 and 13 Hz, averaged across the two resting conditions and across groups, showed the highest alpha activity over these electrodes of the parieto-occipital regions. Additionally, seven centro-parietal electrodes (C2, C4, C6, CP2, CP4, CP6, P2) were selected to represent the parietal ROI of the intact/right hemisphere, and the corresponding homologue electrodes (C1, C3, C5, CP1, CP3, CP5, P1) to represent the parietal ROI of the lesioned/left hemisphere. Finally, six more anterior electrodes (AF4, F2, F4, FC2, FC4, FC6) were chosen for representing the anterior ROI of the right/intact hemisphere, and their homologues (AF3, F1, F3, FC1, FC3, FC5) for representing the anterior ROI of the left/lesioned hemisphere.

To test whether posterior brain damage might affect modulation of alpha and theta power induced by eyes opening, the oscillatory EEG power in both frequency bands was analyzed with separate ANOVAs with *Condition* (eyes-closed, eyes-open), *Hemisphere* (lesioned, intact) and ROI (posterior, parietal, anterior), as within-subject factors and *Group* (hemianopic patients with left lesions, hemianopic patients with right lesions, control patients with anterior lesions and healthy participants) as between-subjects factor. Post-hoc comparisons were performed with Tukey HSD (Spjøtvoll and Stoline, 1973).

4.3. Results

4.3.1. Alpha frequency band

The overall ANOVA on alpha power revealed a significant main effect of *Condition* ($F_{1,44}$ = 128.63; p < 0.001), with higher alpha power in eyes-closed condition (M = 3.90 dB) compared to the eyes-open condition (M = -0.55 dB; p < 0.001) and a significant main effect of *Region* ($F_{2,88}$ = 68.08; p < 0.001), explained by higher power in posterior regions (M = 2.84 dB), relative to parietal regions (M = 0.97 dB; < 0.001) and anterior regions (M = 1.22 dB; p < 0.001; see Fig 12). On the contrary, no significant main effect of *Group* ($F_{3,44}$ = 0.48, p = 0.69) nor significant main effect of *Hemisphere* ($F_{1,44}$ = 128.63; p = 0.216) were found. In addition, the ANOVA showed significant *Condition* x *Group* ($F_{3,44}$ = 4.53; p = 0.007), *Hemisphere* x *Group* ($F_{3,44}$ = 2.94; p = 0.043), *Region* x *Group* ($F_{2,88}$ = 2.30; p = 0.040) and *Condition* x *Region*x*Group* ($F_{6,88}$ = 3.40; p = 0.004) interactions and, more importantly the *Condition* x *Hemisphere* x *Group* ($F_{3,44}$ = 3.68; p = 0.018) interaction was also significant. This significant interaction was explored, collapsing alpha power across *Region*s, performing separate ANOVAs on each group of participants, with *Condition* (eyes-closed, eyes-open) and *Hemisphere* (lesioned, intact) as factors, to compare alpha desynchronization at the opening of the eyes between the hemispheres, independently within each group.

The ANOVA performed on the left-lesioned hemianopic patients revealed a significant main effect of *Condition* ($F_{1,11}$ = 23.93; p < 0.001) with higher alpha power in the eyes-closed condition (M = 4.29 dB) relative to the eyes-open condition (M = 0.86 dB; p = < 0.001), while no significant main effect of *Hemisphere* ($F_{1,11}$= 0.05; p = 0.824) was found. In addition, a significant *Condition* x *Hemisphere* ($F_{1,11}$ = 6.30; p = 0.028) interaction was found, pointing to a higher alpha power in the eyes-closed condition, compared to eyes-open condition in both the lesioned (eyes-closed condition M = 2.63 dB; eyes-open condition M = 0.22 dB; p < 0.001) and the intact hemisphere (eyes-closed condition M = 3.29 dB; eyes-open condition M = 0.06 dB; p < 0.001). Similarly, the ANOVA on the right-lesioned hemianopic patients revealed a significant main effect of *Condition* ($F_{1,11}$ = 24.66; p < 0.001) with higher alpha power in the eyes-closed condition (M = 2.96 dB) relative to the eyes-open condition (M = 0.10 dB; p < 0.001), while no significant main effect of *Hemisphere* ($F_{1,11}$= 0.65; p = 0.439) was found. In addition, a significant *Condition* x *Hemisphere* interaction ($F_{1,11}$ = 7.18; p = 0.021) revealed higher alpha power in the eyes-closed condition, compared to the eyes-open

condition in both the lesioned hemisphere (eyes-closed condition M = 4.17 dB; eyes-open condition M = 1.03 dB; $p < 0.001$) and the intact hemisphere (eyes-closed condition M = 4.39 dB; eyes-open condition M = 0.70 dB; $p < 0.001$). The ANOVA performed on control patients with anterior lesions revealed a significant main effect of *Condition* ($F_{1,11} = 25.54$; $p < 0.001$) with a higher alpha power in the eyes-closed condition (M = 4.15 dB) compared to the eye-open condition (M = -0.78 dB; $p < 0.001$) and a significant main effect of *Hemisphere* ($F_{1,11} = 9.77$; $p < 0.001$) pointing to a higher alpha power in the lesioned hemisphere (M = 2.01 dB) compared to the intact hemisphere (M = 1.36 dB; $p = 0.009$), while the *Condition* x *Hemisphere* ($F_{1,11} = 2.44$; $p = 0.14$) interaction was not significant. Last, the ANOVA on healthy participants revealed a significant main effect of *Condition* ($F_{1,11} = 62.98$; $p < 0.001$) with a higher alpha power in the eyes-closed condition (M = 4.20 dB) compared to the eyes-open condition (M = -2.38 dB; $p < 0.001$), while the main effect of *Hemisphere* ($F_{1,11} = 0.32$; $p = 0.57$) and the *Condition* x *Hemisphere* ($F_{1,11} = 1.09$; $p = 0.317$) interaction were not significant.

These results suggest the occurrence of a significant alpha power desynchronization induced by eyes opening in each group. Nevertheless, to compare the magnitude of the alpha reactivity to the opening of the eyes, we further calculated an index of alpha reactivity by subtracting the mean power in the eyes-open condition to the mean power in the eyes-closed condition (alpha reactivity = mean alpha power eyes-closed *minus* mean alpha power eyes-open) in both the lesioned and the intact hemisphere separately, for each group of participants. Paired t-tests were run, to compare the alpha reactivity indices of each group of patients to the group of healthy participants, separately for the lesioned and the intact hemisphere. Bonferroni correction was used, with significant threshold set at $p = 0.0167$. Left-lesioned hemianopic patients showed a significant reduction of alpha reactivity, compared to healthy participants both in the lesioned (lesioned hemisphere M = 3.14 dB *vs* left hemisphere M = 6.66 dB; $p = 0.001$) and in the intact hemisphere (intact hemisphere M = 3.69 dB *vs* right hemisphere M = 6.49 dB; $p = 0.010$). Similarly, right-lesioned hemianopic patients showed significantly reduced alpha reactivity, relative to healthy participants, both in the lesioned (lesioned hemisphere M 2.41 = dB *vs* right hemisphere M = 6.49 dB; $p < 0.001$) and in the intact hemisphere (intact hemisphere M = 3.30 dB vs left hemisphere, M = 6.66 dB, $p = 0.002$).On the contrary, no significant differences in alpha reactivity were found between the control

group of patients with anterior lesions and the healthy participants both in the lesioned (lesioned hemisphere M = 4.80 dB *vs* left hemisphere M = 6.66 dB; p = 0.024) and in the intact hemisphere (intact hemisphere M = 5.08 dB *vs* right hemisphere M = 6.49 dB; p = 0.099).

Since the overall ANOVA showed also a significant *Condition* x *Region* x *Group* ($F_{6,88}$ = 3.40; p = 0,004) interaction, we further explored the pattern of alpha reactivity, collapsing alpha power across hemispheres and performing four separate ANOVAs for each group of participants, with *Condition* (eyes-closed, eyes-open) and *Region* (posterior, parietal, anterior) as factors, to test alpha desynchronization at the opening of the eyes between the regions, independently within each group.

The ANOVA on left-lesioned hemianopic patients revealed a significant main effect of *Region* ($F_{2,22}$ = 18.03; p < 0.001) with higher alpha power in posterior regions (M = 3.90 dB), relative to parietal regions (M = 2.08 dB; p < 0.001) and anterior regions (M = 1.74 dB; p < 0.001) and a significant main effect of *Condition* ($F_{1,11}$ = 27.93; p < 0.001) with higher alpha power in the eyes-closed condition (M = 4.87 dB) compared to the eyes-open condition (M = 0.86 dB; p < 0.001). The *Condition* x *Region* ($F_{2,22}$ = 1.85; p = 0.180) interaction was not significant. The ANOVA on the right-lesioned hemianopic patients showed a significant main effect of *Condition* ($F_{1,11}$ = 24.66; p < 0.001), with higher alpha power in the eyes-closed condition (M = 2.96 dB) compared to the eyes-open condition (M = 0.11 dB; p < 0.001) and a significant main effect of *Region* ($F_{2,22}$ = 9.68; p < 0.001 with higher alpha power in posterior regions (M = 2.44 dB), relative to parietal regions (M = 0.98 dB; p < 0.001) and anterior regions (M = 1.89 dB; p < 0.001). In addition, a significant *Condition* x *Region* ($F_{2,22}$= 3.73; p = 0.04) interaction was observed. Post-hoc comparisons showed a significant higher alpha power in the eyes-closed condition compared to the eyes-open condition in posterior regions (eyes-closed M = 3.55 dB; eyes-open M = -1.33 dB), parietal regions (eyes-closed M = 2.69 dB; eyes-open M = -0.73 dB) and anterior regions (eyes-closed M = 2.65 dB; eyes-open M = -0.28 dB). In addition, in the eyes open condition, a significant higher alpha power was found in posterior regions compared to parietal regions (p < 0.001) and anterior regions (p < 0.001). For the group of control patients with anterior lesions, the ANOVA showed a significant main effect of *Condition* ($F_{1,11}$ = 25.54; p < 0.001), with higher alpha power in the eyes-closed condition (M = 4.15 dB), compared to the eyes-open condition (M = -0.78 dB; p < 0.001) and

a significant main effect of *Region* ($F_{2,22}$ = 32.70; p < 0.001) with higher alpha power in posterior regions (M = 3.26 dB), compared to parietal regions (M = 0.63 dB; p < 0.001) and anterior regions (M = 1.15 dB; p < 0.001). No significant *Condition* x *Region* ($F_{2,22}$ = 1.16; p = 0.330) interaction was found. Last, the ANOVA on healthy participants revealed a significant main effect of *Condition* ($F_{1,11}$ = 68.89; p < 0.001), with higher alpha power in the eyes-closed condition (M = 4.20 dB) compared to the eyes-open condition (M = -2.37 dB; p < 0.001) and a significant main effect of *Region* ($F_{2,22}$= 14.53; p < 0.001), with higher alpha power over posterior regions (M = 1.74 dB), relative to parietal regions (M = 0.18 dB; p < 0.001) and anterior regions (M = 0.80 dB; p = 0.010). Also, a significant *Condition* x *Region* ($F_{2,22}$ = 41.45; p = < 0,001) interaction was found. The subsequent post-hoc comparisons showed significantly higher alpha power in the eyes-closed condition compared to the eyes-open condition in posterior regions (eyes-closed M = 4.36 dB; eyes-open M = -0.87 dB, p < 0.001), in parietal regions (eyes-closed M = 4.21 dB; eyes-open M = -3,84 dB, p < 0.001) and anterior regions (eyes-closed M = 4.02 dB; eyes-open M = -2.41 dB; p < 0.001). In addition, in the eyes-open condition, alpha power in posterior regions was significantly higher than in parietal regions (p < 0.001) and anterior regions (p < 0.001).

These latter results were in line with the results of the analysis performed to explore the *Condition* x *Hemisphere* x *Group* interaction and confirmed the presence of a significant reduction of alpha power in the three regions of interest within each group of participants with the eyes opening.

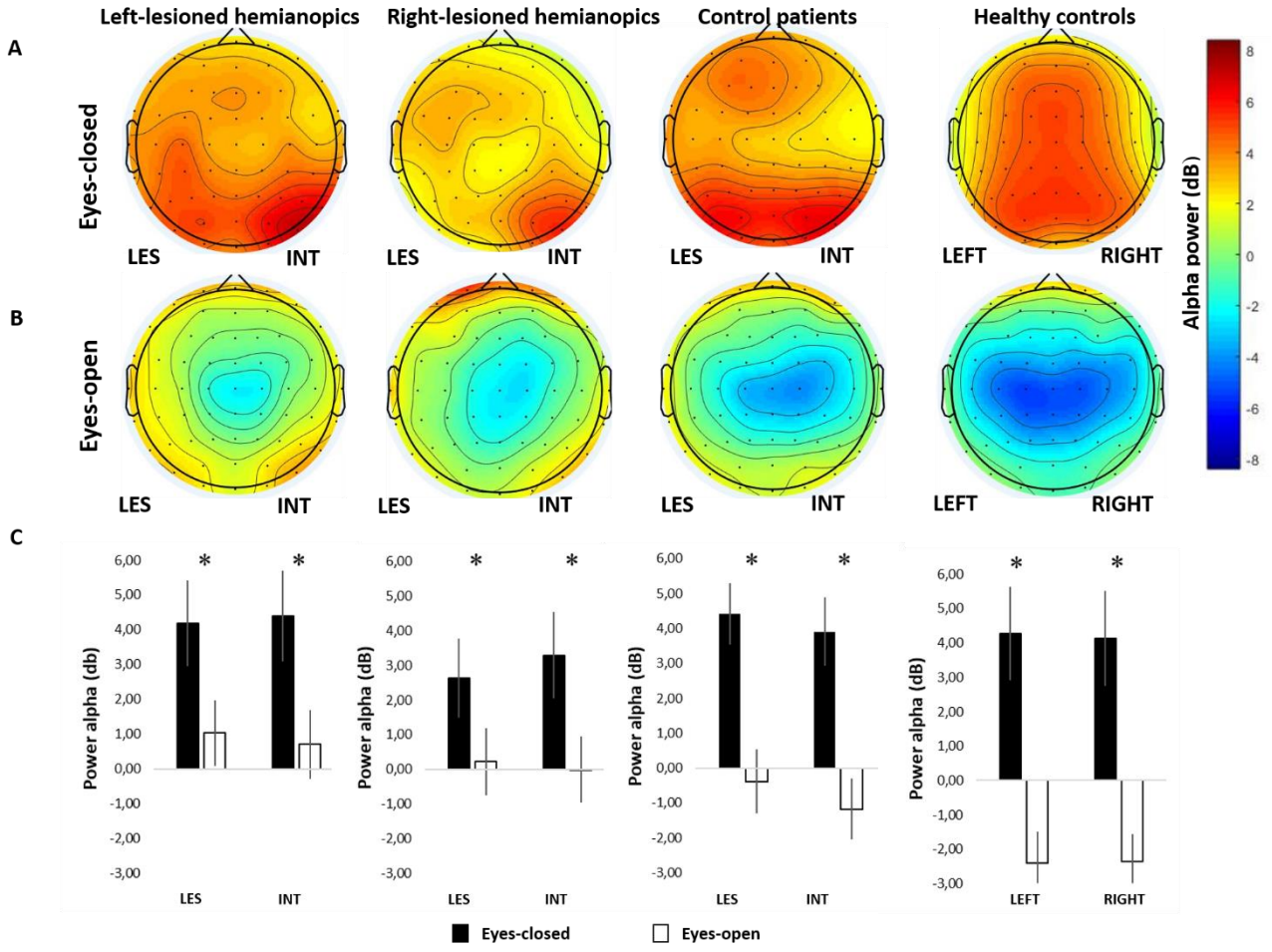

Figure 12. Scalp topographies represent the scalp distribution of the alpha power averaged across each group in the frequency window 7-13 Hz, in the eyes-closed condition (A) and in the eyes-open condition (B). For patients with lesions to the right hemisphere, electrodes were swapped cross-hemispherically, so that the lesioned hemisphere is represented on the left side. (C) Bar histograms show the modulation of mean alpha amplitude in the eyes-closed and the eyes-open conditions, relative to the lesioned/left and the intact/right hemisphere, within each group. Error bars represent standard error; asterisks depict the significant comparisons.

4.3.2. Theta frequency band

The overall ANOVA on theta power revealed a significant main effect of *Group* ($F_{3,44} = 4.16$; $p = 0.011$), with higher theta power in right-lesioned hemianopic patients (M = 3.12 dB) relative to the control patients with anterior lesion (M = -0.24; p = 0.049; see Fig 13) and to the healthy participants (M = -0.28; p = 0.037). A significant main effect of *Hemisphere* ($F_{1,44}$ = 40.76; p = < 0.001), with higher theta power in the lesioned hemisphere (M = 1.66 dB) compared to the intact hemisphere (M = 0. 89 dB; p = 0.001) and a significant main effect of *Region*, with higher theta power in posterior regions (M = 1.87 dB), compared to parietal regions (M = 0.33 dB; p < 0.001) and anterior regions (M = 1.50 dB; p < 0.001), were also found. In contrast, no significant main effect of *Condition* ($F_{1,44} = 3.89$; p = 0.055) was found. Furthermore, the ANOVA revealed a significant *Hemisphere* x *Group* ($F_{3,44}$= 3.88; p = 0.015)

interaction, a *Hemisphere* x *Region* x *Group* ($F_{6,88}$ = 2.48; p = 0.016) interaction and more importantly, a significant *Condition* x *Region* x *Group* ($F_{6,88}$ = 2.88; p = 0.028) interaction. This latter significant interaction was explored, collapsing theta power across hemispheres and performing separate ANOVAs on each group of participants, with *Condition* (eyes-closed, eyes-open) and *Region* (posterior, parietal, anterior) as factors, to test theta changes at the opening of the eyes among these regions, independently within each group.

The ANOVA on left-lesioned hemianopic patients did not show a significant main effect of *Condition* ($F_{1,11}$ = 1.97; p = 0.188), but a significant main effect of *Region* ($F_{2,22}$ = 13.28; p < 0.001) with higher theta power in posterior regions (M = 3.23 dB) compared to parietal region (M = 1.34 dB; p < 0.001) and anterior regions (M = 2.50 dB; p = 0.013) and a significant *Condition* x *Region* ($F_{2,22}$ = 4.66; p = 0.020) interaction. Post-hoc comparisons revealed significantly higher theta power in the eyes-closed condition compared to the eyes-open condition in parietal regions (eyes-closed M = 2.37 dB; eyes-open M = 0.32 dB; p < 0.001) and in anterior regions (eyes-closed M = 3.37 dB; eyes-open M = -1,62 dB; p = 0.003) but not in posterior regions (eyes-closed M = 3.43 dB; eyes-open M = 3.02 dB; p = 0.900). In addition, theta power in the eyes-open condition was significantly lower in parietal regions compared to anterior (p = 0.039) and posterior regions (p < 0.001). The ANOVA on right-lesioned hemianopic patients did not show a significant main effect of *Condition* ($F_{1,11}$ = 0.29; p = 0.600), but a significant main effect of *Region* ($F_{2,22}$ = 6.98; p < 0.001) with higher theta power in posterior regions (M = 3.92 dB) relative to parietal regions (M = 2.30 dB; p = 0.003) and a significant *Condition* x *Region* ($F_{2,22}$ = 8.58; p = 0.002) interaction. Post-hoc comparisons on this interaction did not reveal any significant difference in theta power in the eyes-closed condition compared to the eyes-open condition in parietal regions (eyes-closed M = 2.43 dB; eyes-open M = 2.17 dB; p = 0.535) and in anterior regions (eyes-closed M = 3.30 dB; eyes-open M = 2.96 dB; p = 0.983). On the contrary, a significant lower theta power in the eyes-closed condition (M = 2.80 dB) compared to the eyes-open condition (M = 5.05 dB; p = 0.002) was found in posterior regions. In addition, theta power in the eyes-open condition was significantly higher in posterior regions than parietal regions (p = 0.005) and anterior regions (p = 0.005). In the control patients with anterior lesions, no significant main effect of *Condition* ($F_{1,11}$ = 0.85; p = 0.37) was found. In contrast, a significant main effect of *Region* ($F_{2,22}$ = 11.24; p = 0.004) was evident, with significantly lower theta power in parietal

regions (M = -1.35 dB) compared to posterior (M = 0.40 dB; p = 0.001) and anterior regions (M = 0.21 dB; p = 0.024). The *Condition* x *Region* ($F_{2,22}$ = 2.56, p = 0.045) interaction was also significant. Post-hoc comparisons revealed a significant higher theta power in the eyes-closed condition relative to the eyes-open condition in parietal regions (eyes-closed M = -0.54 dB; eyes-open M = -2.16 dB; p < 0.001). However, no significant difference between the eyes-closed condition and the eyes-open condition was found in both posterior (eyes-closed M = 0,41 dB; eyes-open 0.40 dB; p = 1.00) and anterior regions (eyes-closed M = 0,89 dB; eyes-open M = 0.45 dB; p = 0.073). The ANOVA on healthy participants showed a significant main effect of *Condition* ($F_{1,11}$ = 5.40; p = 0.040) with higher theta power in the eyes-closed condition (M = 0.07 dB) compared to the eyes-open condition (M = -1.32 dB; p = 0.040), a significant main effect of *Region* ($F_{2,22}$ = 13.88; p < 0.001) with significantly lower theta power in parietal regions (M = -0.95 dB) relative to posterior (M = -0.07 dB; p = 0.002) and anterior regions (M = 0.16 dB; p < 0.001) and a significant *Condition* x *Region* interaction ($F_{2,22}$ = 55.25; p < 0.001). Post-hoc comparisons on the *Condition* x *Region* interaction revealed significantly higher theta power in the eyes-closed condition compared to the eyes-open condition in parietal (eyes- closed M = 0.82 dB; eyes-open M = -2.73 dB; p < 0.001) and anterior regions (eyes-closed M = 1.78 ; eyes-open M = 1.14 dB; p < 0.001 dB), but no significant difference between the two conditions was found in posterior regions (eyes-closed M = -0.31 dB; eyes-open M = 0.17; p = 0.583). In addition, theta power in the eyes-open condition was lower in parietal regions than in anterior regions (p < 0.001).

Overall, these results suggest differences between groups in modulations of theta power induced by eyes opening in the three regions examined. More specifically, no changes between the eyes-closed and the eyes-open conditions were found in the posterior regions in all groups, with the exception of right lesioned hemianopic patients, who showed an atypical increase in theta power at the opening of the eyes, compared to the eyes-closed condition. Looking at the parietal regions, on the contrary, all groups, except for right-lesioned hemianopic patients, showed a significant desynchronization at the opening of the eyes. Therefore, to compare the magnitude of theta desynchronization, an index of theta reactivity at the opening of the eyes was calculated (theta reactivity = mean theta power eyes-closed *minus* mean theta power eyes-open) in the parietal regions, for left-lesioned hemianopic patients, control patients with anterior lesions and healthy participants. Paired t-tests were

performed to compare the reactivity index of each group of patients with the healthy participants group. No difference on the magnitude of theta reactivity was found between groups (all ps > 0.132). Finally, in anterior regions, only left-lesioned hemianopic patients and healthy participants showed a significant desynchronization, while no change in theta power at the opening of the eyes was found in right-lesioned hemianopic patients and control patients with anterior lesions. Therefore, theta reactivity index (theta reactivity = mean theta power eyes-closed *minus* mean theta power eyes-open) was calculated only in left-lesioned hemianopic patients and healthy participants. Paired t-test revealed no significant difference in the magnitude of theta reactivity ($p = 0.179$).

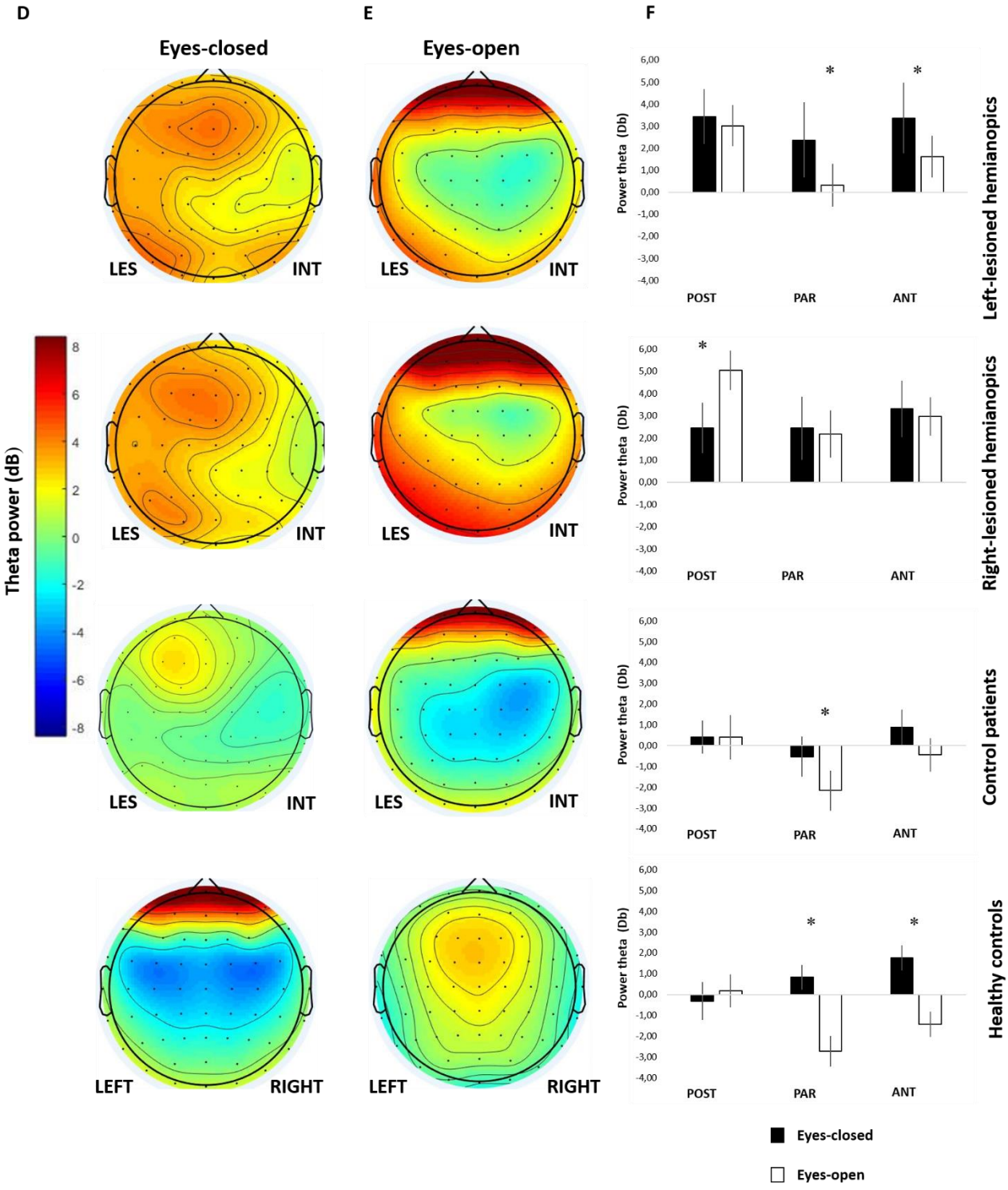

Figure 13. Scalp topographies represent the scalp distribution of the theta power averaged across each group in the frequency window 4-6 Hz, in the eyes-closed condition (D) and in the eyes-open condition (E). For patients with lesions to the right hemisphere, electrodes were swapped cross-hemispherically, so that the lesioned hemisphere is represented on the left side. (F) Bar histograms show the modulation of mean theta amplitude in the eyes-closed and the eyes-open conditions, relative to posterior, parietal and anterior ROIs, within each group. Error bars represent standard error; asterisks depict the significant comparisons.

4.4. Discussion

The present study compared eyes-closed and eyes-open resting-state conditions in patients with posterior brain lesions with visual field defects and age-matched control groups of patients with more anterior lesions and healthy participants. The results showed that all groups presented a significant desynchronization of alpha power at the opening of the eyes, across all scalp regions. Specifically, decreased alpha power during the eyes-open condition compared to the eyes-closed condition was found in posterior, parietal and anterior sites, in both the left and the right hemispheres. Nevertheless, alpha reactivity induced by eyes-opening was reduced in both the lesioned and the intact hemisphere of left- and right-lesioned hemianopic patients. This is in line with the study reported in the chapter 2 demonstrating that left and right posterior brain lesions selectively impair alpha oscillatory parameters during eyes-closed resting state, resulting in a slowdown of IAF and an interhemispheric power imbalance, in favor of the intact hemisphere (Pietrelli et al., 2019). Importantly, this result shows that, regardless alterations to the baseline alpha oscillatory activity due to posterior lesions, hemianopic patients retain a residual reactivity in the alpha range to the opening of the eyes, which is evident, but reduced after damage to the posterior cortices. This residual alpha oscillatory reactivity seems also in agreement with previous reports showing that hemianopic patients can retain stimulus-related alpha modulations, induced by the presentation of stimuli in the blind field (Grasso et al., 2018; Sanchez-Lopez et al., 2019). Importantly, the reduced alpha reactivity seems independent from the reduced visual input, consequent to the presence of visual field defect. Indeed, alpha desynchronization has been consistently reported also at the opening of the eyes in complete darkness (Ben-Simon et al., 2013) and in blind individuals (Hüfner, Stephan, Flanagin, Deutschländer, Stein, Kalla, Dera, 2009).

Converging evidence report that eyes-closed and eyes-open conditions correspond to distinct neurophysiological states and functional connectivity patterns (Jao, Vértes, Alexander-Bloch, Tang, Yu, Chen, and Bullmore, 2013; Xu, Xiong, Xue, Tian, Peng, Zhang, Li, Wang, and Yao, 2014). More precisely, eyes-closed resting state has been linked to a state of greater network integration, with reduced modularity and increased global efficiency (Bianciardi, Fukunaga, van Gelderen, Horovitz, de Zwart, and Duyn, 2009; Xu et al., 2014). In contrast, eyes-open resting-state has been associated with greater modularity, which is thought to

facilitate increased local efficiency, subserving task-dependent processing (Xu et al., 2014; Allen, Damaraju, Eichele, Wu, and Calhoun, 2018). In this perspective, the typical alpha desynchronization in the transition from the eyes-closed to the eyes-open condition might represent a widespread cortical activation, supporting the focal decreases in non-alpha bands, related to local processing aiming at gathering visual information (Marx et al., 2003; Barry et al., 2007; Barry and De Blasio, 2017).

Notably, in the current findings, lesions to posterior cortices similarly affect alpha reactivity in both hemianopic patients with left and right lesions. This is in contrast with previous findings on hemianopic patients showing that posterior right lesions led to more severe alpha oscillatory impairments, with stronger IAF reduction and interhemispheric power imbalance, relative to posterior left lesions (Pietrelli et al., 2019). However, in the present findings, a peculiar pattern of reactivity at the opening of the eyes in hemianopic patients with right lesions was found in the theta frequency range. More precisely, while healthy participants demonstrated a typical desynchronization in the theta range over centro-anterior regions at the opening of the eyes (Barry et al., 2007; Barry and De Blasio, 2017), right-lesioned hemianopic patients revealed no significant change over parietal and anterior regions of the scalp and an atypical increase of theta power over posterior regions, in the transition from eyes-closed to eyes-open resting state. On the contrary, hemianopic patients with left lesions showed a regular pattern of theta desynchronization, just like healthy participants.

Alterations in the theta range after brain damage has been consistently reported in eyes-closed resting state. Specifically, increased theta power in perilesional areas has been described in patients with stroke (Butz et al., 2004; Chu et al., 2015; Dubovik et al., 2012; Laaksonen et al., 2013; Tecchio et al., 2005), likely reflecting reorganization of the lesioned cortices (Carmichael and Chesselet, 2002; Rabiller et al., 2015). Previous reports comparing hemianopics patients and control patients with anterior lesions also showed that post-lesional theta power increase is evident after lesions both to posterior and anterior cortices (Pietrelli et al., 2019). However, the current findings show that theta reactivity to the opening of the eyes seems selectively compromised after posterior right lesions. Interestingly, in patients with anterior lesions, theta power showed a global desynchronization. However, over the lesion sites (i.e., over anterior regions), theta power showed no significant desynchronization. This seems to suggest that patients with anterior lesions retain reactivity to the opening of the

eyes in the theta range, but they show a local impairment in desynchronizing theta power over the site of the lesion. Notably, theta power has been associated with distributed sources in fronto-temporal and fronto-central cortices (Iramina, Ueno, and Matsuoka, 1996; Ishii, Shinosaki, Ukai, Inouye, Ishihara, Yoshimine, Hirabuki, 1999). These distributed theta sources suggest that lesions to anterior cortices might focally impair theta reactivity, sparing theta desynchronization over non-lesioned sites. In contrast, hemianopic patients with right posterior lesions showed a widespread alteration in theta reactivity at the opening of the eyes, which adds to their reduced alpha reactivity. This result seems in line with the finding reported in chapter 3, showing that right posterior lesions selectively reduced functional connectivity in the alpha range, while increasing functional connectivity in the theta range during eyes-closed resting state. The dysfunctional reactivity in the theta range observed in the present study might reflect the disruption of the typical focal oscillatory changes occurring at the opening of the eyes, which have been associated with stimulus processing and, hence, to low-level unstructured responses to visual stimuli during eyes-open resting state (Barry and De Blasio, 2017; Gevins, Smith, McEvoy, and Yu, 1997; Grillon and Buchsbaum, 1986).

The combination of impairments in the alpha and the theta range observed in hemianopic patients with right lesions suggests the presence of a stronger impairment in functional reactivity to the opening of the eyes, compared to hemianopic patients with left lesions, involving both global and local processes. Indeed, right posterior lesions, on the one hand, weaken the reduction of alpha power, reflecting the widespread cortical activation, which gates and controls visual inputs at the opening of the eyes, facilitating visual processing; on the other hand, right posterior lesions also impair focal theta reduction, which is linked with modular processing and local cortical activations (Barry and De Blasio, 2017; Gevins et al., 1997; Grillon and Buchsbaum, 1986). This seems in line with the notion that alpha oscillations propagating from posterior visual cortices to higher-order cortical sites, might play a special role in coordinating widespread oscillatory activity and orchestrating focal processing in non-alpha frequency bands, which might support visual processing at the opening of the eyes (Barry and De Blasio, 2017). The observation that this mechanism is more severely impaired after posterior lesions to the right hemisphere might be in line with the previously mentioned (see chapters 2 and 3) theories that posit a dominance of the right hemisphere in spatial

representation (Heilman and Van Den Abell, 1980) and in balancing the interhemispheric inhibition (Kinsbourne, 1977).

Overall, the present findings corroborate the hypothesis that neural oscillations in the alpha frequency band are intrinsic of the posterior cortices and that posterior brain damage have a considerable impact on neural mechanisms supporting alpha power reactivity. Indeed, alpha reactivity to the opening of the eyes was shown to be reduced in hemianopic patients with both left and right lesions to posterior cortices. This may indicate that hemianopic patients are characterized by reduced task-independent activation of the visual system.

Chapter 5: Unseen distractors delay saccadic latency in left-lesioned hemianopic patients

5.1. Introduction

Although hemianopic patients, after lesions to the primary visual pathway, do not demonstrate conscious vision in the half of their visual field contralateral to the lesions, the ability to discriminate above the chance level the presence or the features (e.g., shape, color and emotion) or to localize (by pointing or performing saccades) stimuli presented in the blind field in forced choice tasks has been reported in a limited number of patients with visual field defect and has been defined "blindsight" (Blythe et al., 1987; Perenin and Jeannerod, 1975; Lawrence Weiskrantz et al., 1974; Pöppel et al., 1973). However, blindsight seems to represent a peculiar phenomenon, since hemianopic patients do not typically show above chance performance when guessing about the presence or the features of stimuli presented in their blind field. Nevertheless, brain lesions commonly found in hemianopic patients without blindsight usually spare subcortical and cortical structures, independent from the primary visual pathway, that are relevant for visual processing and might mediate residual visual abilities (Tamietto and Morrone, 2016). In line, previous evidence showed that hemianopic patients without blindsight could show implicit visual processing for specific categories of unseen stimuli. For instance, alpha desynchronization in posterior visual cortices has been observed for the presentation of unseen motion stimuli, whereas no alpha desynchronization was found with unseen static stimuli (Grasso et al., 2018). In addition, hemianopic patients without blindsight showed behavioral (Bertini et al., 2013; Bertini et al., 2018; Bertini et al., 2017) and electrophysiological (Cecere et al., 2014) evidence of implicit visual processing when unseen fearful faces were presented in their blind visual field, but not for the presence of happy or neutral faces. The specificity of the residual abilities observed in hemianopic patients without blindsight suggests that spared subcortical visual pathways, which retain the ability of processing these categories of stimuli without awareness, might be involved in the implicit visual processing of these unseen stimuli. Specifically, these implicit visual abilities have been attributed to the visual pathways conveying visual information from the retina, to the Superior Colliculus (SC) and then projecting to subcortical (i.e., the Pulvinar and the Amygdala) and cortical (dorsal extra-striate areas) structures, responsive to visual stimuli,

usually spared in hemianopic patients (Bertini et al., 2013; Bertini et al., 2018; Bertini et al., 2017).

In addition to its role in mediating implicit visual processing, a wide range of evidence report the relevance of the SC in the generation and programming of saccadic eye-movements related to both covert and overt attention (Krauzlis et al., 2013).As a consequence, due to the shared neural circuits subserving both implicit visual processing and saccadic eye-movements, it is possible that hemianopic patients without blindsight could show implicit processing for simple unseen visual stimuli in tasks requiring the implementation of saccades, and, therefore, involving the activity of the SC.

Evidence on healthy participants have revealed a pivotal contribution of the SC and other relevant oculomotor structures independent from V1, such as FEF (Dorris, Olivier, and Munoz, 2007; Sommer and Wurtz 2004a; 2004b), in mediating a remote distractor effect (RDE; Walker and Benson, 2013; Walker, Deubel, Schneider, and Findlay, 1997; Walker, Mannan, Maurer, Pambakian, and Kennard, 2000; Walker, Kentridge, and Findlay 1995; Findlay and Walker 1999) during a saccadic localization task. RDE refers to the observation that saccadic latency towards targets is delayed when concurrent distractors are presented in the opposite hemifield (Walker and Benson, 2013; Walker et al., 1997; 2000; Walker et al., 1995; Findlay and Walker, 1999). This effect has been attributed to distractor-related interference in saccade planning (Findlay and Walker, 1999; Walker et al., 1997; Ludwig, Gilchrist, and McSorley, 2005). More precisely, it has been proposed that mutually inhibitory mechanisms between the fixation and saccade initiation subpopulations of the buildup neurons of the SC might account for the RDE (Findlay and Walker, 1999; Walker et al., 1997; Gandhi and Keller, 1999). Alternatively, RDE has been explained as a mechanism of long-range lateral inhibition between neural populations encoding target and distractor positions either within the SC (Dorris et al., 2007; Ludwig et al., 2005) or within the FEF (Dorris et al., 2007; Sommer and Wurtz 2004a; 2004b).

Although the RDE effect has been widely documented in healthy participants, evidence of delayed saccadic latencies in the presence of distractors in the blind field in hemianopic patients have been inconclusive (Rafal, Smith, Krantz, Cohen, and Brennan, 1990; Walker et al., 2000; Van der Stigchel, Zoest, Theeuwes, and Barton, 2008). Therefore, the present study

aimed to test whether unseen visual distractors presented in the blind field can be processed in the absence of awareness in hemianopic patients without blindsight and can delay saccadic initiation towards targets in the intact field, thus demonstrating the presence of an RDE effect.

In addition, since the FEF has a critical role in the generation and planning of saccadic eye-movements and seems to participate in mediating the RDE (Dorris et al., 2007; Sommer and Wurtz 2004a; 2004b) possible hemispheric differences should be taken into account. Indeed, the right hemisphere has reportedly a prominent role in visuospatial abilities (Kinsbourne, 1987; Heilman and Valenstein, 1979; Heilman and Van Den Abell, 1980; Corbetta and Shulman, 2011) and left and right FEF and PPC show strong asymmetries in spatial representation and attentional allocation (Duecker and Sack, 2015).

To this aim, two groups of hemianopic patients with left or right posterior lesions were separately tested in a saccadic localization task, in which they had to make saccadic eye-movements toward simple visual stimuli presented in their intact visual field while visual distractor stimuli could be presented in the blind visual field.

5.2. Methods

5.2.1. Participants

Two groups of participants took part to the study: eight patients (5 males, mean age = 50.1 years, mean time since lesion onset = 11.9 months) with visual field defect due to lesions to the left posterior cortices, nine patients with visual field defect due to lesions to the right posterior cortices (8 males, mean age = 55.8 years, mean time since lesion onset = 12.0 months). No differences between the groups were found relative to age ($F_{1,15} = 0.79$; $p = 0.389$) or time since lesion onset ($F_{1,15} = 0.00$; $p = 0.989$). Clinical details are reported in Table 4.

ID	Sex	Age	Onset	Lesion site	Visual Field Defect	Aetiology
EMI01	F	57	28	Left Fronto-Temporo-Insular	Right hemianopia	AVM
EMI02	M	69	5	Left Occipital	Right hemianopia	Ischaemic
EMI03	M	51	5	Left Fronto-Temporo-Occipital	Right hemianopia	Abscess
EMI04	M	45	42	Left Fronto-Parieto-Temporal	Right hemianopia	Hemorragic
EMI05	M	41	2	Left Occipital	Lower right quadrantopia	Ischaemic
EMI06	F	32	4	Left Parieto-Occipital	Right hemianopia	Ischaemic
EMI07	F	55	3	Left Fronto-Temporo-Parieto-Occipital	Right hemianopia	Ischaemic

EMI08	M	51	6	Left Temporo-Parietal	Right hemianopia	AVM
EMI09	M	56	3	Right Occipital	Left hemianopia	Ischaemic
EMI10	M	30	54	Right Temporal	Left hemianopia	Hemorragic
EMI11	M	43	1	Right Parieto-Occipital	Left hemianopia	AVM
EMI12	M	76	7	Right Occipital	Left hemianopia	Abscess
EMI13	M	57	17	Right Fronto-Temporo-Parietal	Left hemianopia	Ischaemic
EMI14	F	70	15	Right Temporo mesial	Left hemianopia	Hemorragic
EMI15	M	59	6	Right Temporo-Occipital	Left hemianopia	Ischaemic
EMI16	M	67	2	Right Parieto-Occipital	Left hemianopia	Ischaemic
EMI17	M	44	1	Right Front-Occipital	Left hemianopia	TBI

Table 4. Summary of clinical data of all patients that took part to the study. Legend: M = Male; F = Female; AVM = Arteriovenous Malformation; TBI = Traumatic Brain Injury

Mapping of brain lesions was performed using MRIcro. Lesion documented by the most recent clinical CT or MRI were traced onto the T1-weighted MRI template from the Montreal Neurological Institute with MRIcro software (Rorden and Brett, 2000; Rorden et al., 2007) with the exception of EMI05, EMI07, EMI08, EMI11, EMI13, EMI14, EMI16 and EMI17whose MRI scans were not available. Lesions volumes were computed for each patient and the extent of the lesions were compared between the two groups, revealing no significant differences (one-way ANOVA, $F_{1,7} = 1.45$; $p = 0.267$) between left- and right-lesioned hemianopic patients. Participants showed normal or corrected-to-normal visual acuity. Patients were informed about the procedure and the purpose of the study and gave written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Regional Health Service Romagna (CEROM; n.2300).

5.2.2. Experimental procedure

Participants sat in a dark and sound-attenuated room, in front of a semi-circular experimental apparatus at a distance of 70 cm from the center of the apparatus (see below), with their chin on a chinrest and wearing the head-mounted unit of the Chronos Eye-Tracking Device (C-ETD, Chronos Vision GmbH, Germany, www.chronos-vision.de). All the participants performed two two-alternative forced-choice tasks to test the presence of blindsight and a saccadic localization task (see below).

5.2.3. Experimental apparatus

The experimental apparatus was a black semi-circular structure, with five LED lights placed at the eye level. Specifically, one green LED light was placed at the center, while four red LED lights were placed at 8° and 24° of eccentricity to the left and right of the central green LED light. Stimulus presentation was controlled by a custom routine on MATlab.

In the saccadic localization task, the position of the left and right eye was monitored online and recorded by the Chronos Eye-Tracker Device, which tracks horizontal and vertical eye-movements at 400 Hz. Two infrared cameras are mounted on a headset, pointing on two semi-reflective mirrors. Specifically, only infrared light is reflected by the mirrors, whereas visible light can pass throughout without any problem. In this way, participants can freely see all the visual field while the two side cameras can record eye-movements. A calibration procedure was performed before the saccadic localization task. During the calibration procedure, each participant had to fixate in a sequential order the central green LED light and four points placed ten degrees to the left, right, above and below of the green LED light. In this way, the eye-tracking device was able to provide a coordinate system independent from the participant head position.

5.2.4. Two-alternative forced choice tasks

In order to verify that patients had no awareness of the stimuli presented in their blind field and no ability to detect them above chance, i.e. they had no form of blindsight, they underwent two separate two-alternative forced choice tasks (2AFC), where they were asked to detect, by guessing, the presence of stimuli presented in their blind field. Specifically, in the first 2AFC task participants have to guess the presence of stimuli randomly presented or not at 8° in their blind field, whereas in the second 2AFC task they were asked to guess the presence of stimuli randomly presented or not at 24° in their blind field. Before each trial, the central green LED light was turned on and the experimenter verified that the patients' gaze was on the central green LED light. When patients' gaze was aligned to the green LED light, the experimenter started the trial. At the beginning of the trial, the central green LED light was turned on for a variable time between 50 and 150 ms. Then, it was turned off and, after a variable time interval between 100 and 300 ms, the red LED light was turned on for 100 milliseconds, at 8° or 24° in the blind visual field, in the first and second 2AFC task, respectively. In half of the trials a

stimulus appeared, while in the remaining half no stimulus was presented. Participants had to guess the presence or absence of visual stimuli and to provide their response verbally, always keeping their gaze on the central green LED light. For each target locations, patients performed two blocks (80 trials per block).

The number of correct responses, for each target position, was computed and was compared to the chance level (50% correct responses) using a binomial test. Statistical validity of the patient's performance was established by computing the two-tailed probability value of the number of correct responses on the binomial distribution.

5.2.5. Saccadic localization task

In the visual localization task, patients had to maintain their gaze on the green central LED light and move their gaze, as fast and as accurate as possible, toward target red LED lights presented in their intact field, while ignoring distractors presented in their blind field. After each saccadic eye-movement, patients had to move their gaze back to the central green LED light.

At the beginning of each trial, the central green LED light was turned on and the experimenter verified that the patients' gaze was on the central green LED light. When patients' gaze was aligned to the green LED light, the experimenter started the trial. At the beginning of each trial, the central green LED light stayed on for a variable time between 50 and 150 ms. Then, the central green LED light turned off and, after a time interval between 100 and 300 ms, a red LED light was turned on for 100 ms at 8° or 24° in the intact visual field (target). Each target, could be presented alone (unilateral target), or coupled with a concurrent red LED light in the blind visual field presented at 8° (8° distractor) or at 24° (24° distractor). This resulted in six possible stimuli combination, i.e., 3 with the target at 8° in the intact field (unilateral target at 8°, target at 8° and distractor at 8°, target at 8° and distractor at 24°) and 3 with the target at 24° in the intact field(unilateral target at 24°, target at 24° and distractor at 8°, target at 24° and distractor at 24°). In addition, catch trials were also presented (i.e., no red LED lights were turned on) to avoid anticipatory saccades. Specifically, hemianopic patients failed to inhibit the start of a saccadic eye-movement only on the 5.5% of the catch trials (left-lesioned hemianopic patients = 5%, right-lesioned hemianopic patients = 6%).

The task consisted of 6 blocks of 40 trials each. For each target position, each block consisted of 5 unilateral target trials, 5 trials in which the distractor was presented at 8° and 5 trials in which the distractor was presented at 24°. In addition, 10 catch trials were also presented in each block. Trials' order was randomized.

5.2.6. Data processing and statistical analysis

Eye gaze position over time was extracted from the infrared videos with the build-in Iris software. Saccadic eye-movements were then identified from the eye-gaze position data as changes in position faster than 60°/sec for more than 20 ms and that lead to more than 3,5° of displacement. Saccadic eye-movements starting from more than 3,5° away from the central green LED light and eye movements towards the blind field were excluded from the analysis. Saccadic latency was then calculated as the time interval between the target onset and the starting time of the saccadic eye-movement. Saccades with a saccadic latency below 80 ms or above 1000 ms were discarded, reflecting an anticipatory or not related to stimulus presentation saccadic eye-movement. Finally, only saccadic eye-movements with saccadic latency between two standard deviations from the average were included in the analysis (11% of the total trials were discarded).

Saccadic latencies were analyzed with STATISTICA 11 software (StatSoft; Version 12.0; www.statsoft.com). Repeated measure ANOVAs were run for each of group separately, with *Target Position* (8° and 24°) and *Condition* (unilateral target, 8° distractor, 24° distractor) as within-subject factors. Post-hoc comparisons were then analyzed with the Newman-Keuls test.

5.3. Results

Results relative to the 2AFC tasks revealed that no patient showed significant above chance level responses in discriminating the presence of a visual stimulus either at the 8° or at the 24° in the blind field (all ps > 0.075).

Concerning the saccadic localization task, the ANOVA on the saccadic latencies on left-lesioned hemianopic patients showed a significant effect of *Condition* ($F_{2,14} = 15.91$, $p < 0.001$). Specifically, saccadic latency was significantly slower when a distractor was placed at 8° (M = 275 ms) compared to the condition in which no distractor was presented (M = 264

ms, $p < 0.001$) or to the condition in which a distractor was presented at 24° (M = 267 ms, $p = 0.002$). Finally, no significant difference was found in the saccadic latency when a distractor was presented at 24° compared to when no distractor was presented ($p = 0.099$). Both the main effect of *Target Position* ($F_{1,7} = 1.44$, $p = 0.269$) and the interaction *Condition x Target Position* ($F_{2,14} = 2.12$, $p = 0.157$) were not significant. Therefore, left-lesioned hemianopic patients showed a significantly slower saccadic latency for saccades toward the intact field when a distractor in the blind field was presented at 8° compared to when no distractor was presented (see Fig. 14).

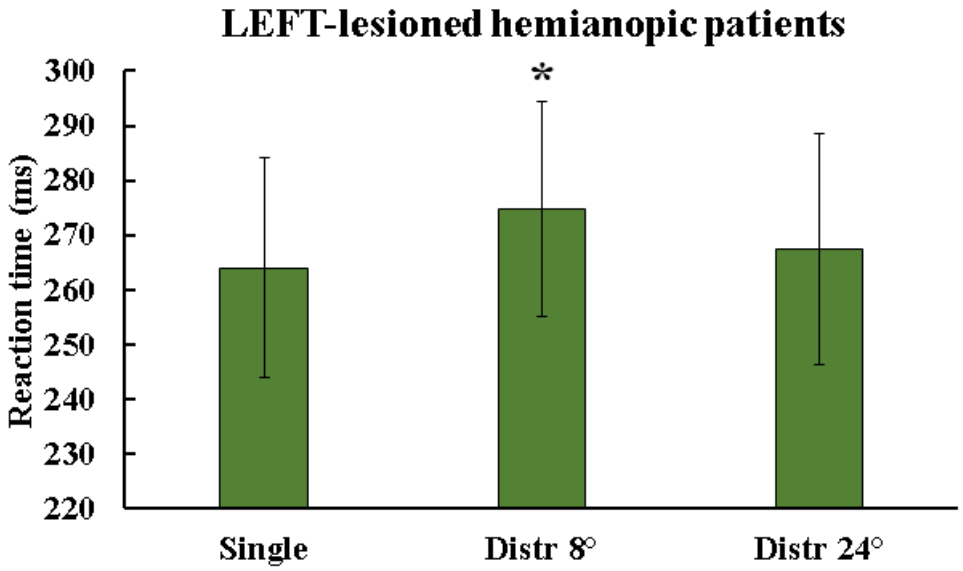

Figure 14. Bar plots show mean reaction times values for the three stimulation conditions averaged across the two targets condition in the left-lesioned hemianopic patients' group. Error bars represent SEM. Asterisks denote significant comparisons

On the contrary, the ANOVA on the saccadic latency for the right-lesioned hemianopic patients showed no significant main effect of *Condition* ($F_{2,16} = 0.38$, $p = 0.690$) or interaction between *Condition* and *Target Position* ($F_{2,16} = 0.12$, $p = 0.890$). Moreover, also the main effect of *Target Position* was not significant ($F_{1,8} = 0.84$, $p = 0.387$). These findings suggest that right-lesioned hemianopic patients showed no significantly slower saccadic latency for saccades toward the intact field when a distractor in the blind field was presented compared to when no distractor was presented.

5.4. Discussion

Hemianopic patients without blindsight with left and right lesions showed a different pattern of saccadic responses in the saccadic localization task with unseen distractors. More precisely, left-lesioned hemianopic patients showed the presence of a RDE, with delayed latencies for saccades towards targets in the intact visual field, when concurrent unseen distractors were presented in the blind field at the 8°, compared to the condition where no distractor was presented. On the contrary, right-lesioned hemianopic patients showed no modulation of the presentation of unseen distractors on saccadic latencies for saccades toward targets in the intact visual field.

The presence of RDE in left-lesioned hemianopic patients without blindsight reveals that simple visual stimuli presented in the periphery of the blind visual field can be processed in the absence of awareness and can interfere with saccadic initiation towards stimuli in the intact visual field. Since RDE has been attributed to inhibitory mechanisms within the SC (Findlay and Walker, 1999; Walker et al., 1997; Gandhi and Keller, 1999) and a widely distributed subcortical and cortical network involving FEF (Dorris et al., 2007; Sommer and Wurtz 2004a; 2004b), spared activity in this circuit might account also for the implicit visual processing for unseen distractors, observed in left-lesioned hemianopic patients in these findings. In line, implicit abilities in processing specific categories of unseen stimuli in the absence of awareness has been previously described in hemianopic patients without blindsight and has been related to the activity of spared subcortical circuits involving the SC and subcortical and cortical structures relevant in visual processing (Bertini et al., 2013; Bertini et al., 2017; 2018; Cecere et al. 2014; Anders et al., 2004).

Notably, previous studies using similar experimental paradigms on patients with visual field defects, failed to find any consistent remote distractor effect for unseen distractors on saccades towards targets in the intact visual field (Rafal et al., 1990; Walker et al., 2000; Van der Stigchel et al., 2008). While RDE was first demonstrated in three left-lesioned patients by Rafal (1990), subsequent studies testing wider samples of hemianopic patients did not find any interference effect of unseen distractors (Walker et al., 2000) or reported RDE only in a few cases (i.e., two out of six patients tested; Van der Stigchel et al., 2008). Different reasons can account for the incongruence between current and previous results. First, previous studies

used small sample sizes and did not take into account possible differences between left- and right-lesioned hemianopic patients, which have been proven relevant in this study in demonstrating RDE. For instance, in the study by Walker (Walker et al., 2000) only two left-lesioned hemianopic patients were tested and this might account for the lack of any consistent RDE. In addition, several methodological differences might explain previous inconsistent findings. For instance, saccadic latency might be affected by the nature of the targets (Liversedge, Gilchrist, and Everling, 2011) by the task instructions (i.e., by focusing more on speed or accuracy; Reddi and Carpenter, 2000), by stimulus probability (Carpenter and Williams, 1995) and stimulus spatial frequency (Ludwig, Gilchrist, and McSorley, 2004). In line, a possible mechanism explaining differences in the present and the previous findings is related to stimulus duration. Indeed, in previous studies targets and distractors lasted between 500 and 1000 ms, whereas in the current study they had a duration of 100 ms. It is reasonable that a shorter duration of the stimuli might lead to a raw processing of visual stimuli, increasing the time for the oculomotor system to resolve the competition between the target and the distractor stimuli and, thus, inducing a delay in saccade initiation. Furthermore, in the current paradigm a variable time interval between fixation offset and target presentation was used to ensure attentional disengagement. This reduced mean saccadic latencies, avoiding possible ceiling effects which could mask the presence of RDE.

In the present findings, RDE was found for saccadic eye-movements towards targets in the intact visual field only when a distractor was presented at 8° in the opposite blind visual hemifield. This is in line with previous evidence showing a reduction of RDE, at the increase of the eccentricity of the distractors (Walker et al., 1997; Honda, 2005; Findlay and Walker, 1999).

Notably, the present findings did not reveal any RDE for hemianopic patients with right lesions, thus suggesting a contribution of the right hemisphere in mediating the interference of a distractor on saccadic initiation. This seems in line with the widely documented dominance of the right hemisphere in spatial representation (Heilman and Van Den Abell, 1980) and in balancing interhemispheric activity (Kinsbourne, 1977). Interestingly, the FEF, which are involved in programming saccadic eye-movements and play a critical role in RDE, reportedly shows a strong left-right asymmetry in the control of the visual field (Hung et al., 2011; Grosbras and Paus, 2003; 2002; Chanes et al., 2012). More specifically, it has been

shown that the right FEF seem to mediate attentional shifts to both contra- and ipsi-lateral hemifields, whereas the left FEF mediate attentional shift only to the contralateral hemifield (Grosbras and Paus, 2003; Chanes et al., 2012; Duecker et al., 2013; Duecker and Sack, 2015). This is in line with a possible contribution of the right FEF on RDE in hemianopic patients. More specifically, the present findings show that only when the right hemisphere is intact (i.e., in left-lesioned hemianopic patients), unseen distractors in the blind right visual field interfere with saccades towards the intact left visual field, in line with the hypothesis that right FEF might retain spatial representation of both targets in the left intact visual field and distractors in the blind right visual field (Duecker and Sack, 2015), thus contributing in RDE. In contrast, when the right hemisphere is lesioned, the spared left hemisphere, which retains spatial representation limited to the contralateral visual field, seems to be insufficient to demonstrate RDE.

Overall, the RDE for unseen stimuli observed in the present study corroborates the hypothesis that hemianopic patients without blindsight might demonstrate implicit visual processing in the absence of awareness, for stimuli encoded by alternative visual circuits independent from V1. Although the SC seems to play a pivotal role in mediating both the effects of a distractor in delaying saccadic latencies and the visual processing of unseen stimuli, the contribution of cortical structures participating to the oculomotor networks, such as FEF and PPC, might be relevant for the occurrence of RDE.

Chapter 6: General discussion

All primates, including humans, depend heavily on sight. Several parts of the brain are involved in the processing of visuospatial information, both in subcortical and cortical brain areas. A way to better understand the functionality of the human visual system is the study of patients with hemianopia. In hemianopia, patients lose the conscious vision in a part of the visual field due to the lesion of posterior visual cortices. Consequently, hemianopic patients represent a perfect neuropsychological model to investigate the functionality of the visual system. Furthermore, investigating how the visual system works in hemianopic patients can help to characterize deficits and residual abilities after posterior brain lesion. In the previous chapters, four studies have been presented, in which the functionality of the human visual system after posterior brain lesions has been investigated in hemianopic patients, exploring both the electrophysiological patterns of post-lesional activity and the residual implicit visual processing.

In previous literature, the electrophysiological correlates of the functionality of the visual system after a posterior lesion were investigated by recording the visual-evoked potentials evoked by the presentation of stimuli in the blind visual field, but with poor results. In recent studies, the oscillatory nature of the brain's electrophysiology was exploited to record the electrophysiological oscillatory activity induced by the presentation of stimuli in the blind field (Grasso et al., 2018; Bollini et al., 2017; Sanchez-Lopez et al., 2019). Among all the brain frequencies, oscillatory activity in the alpha band (7-13 Hz) over occipito-parietal regions is the dominant frequency of the visual system (Rosanova et al., 2009) and shows an active role in shaping visual perception and spatial attention in healthy participants (Klimesch et al., 2007; Jensen and Mazaheri, 2010). In addition, the spontaneous alpha activity recorded during the resting-state, i.e. without any stimulus presentation, is able to predict the behavioral performance in visuospatial task in healthy participant (Klimesch 1997; Klimesch, 1999; Cecere et al., 2015; Mathewson et al., 2009; Samaha and Postle, 2015), therefore suggesting that it might reflect the functionality of the visual system.

In the study presented in chapter 2 EEG oscillatory activity was recorded during eyes-closed resting state, left- and right-lesioned hemianopic patients showed a slowdown of the speed of alpha oscillation in both the intact and the lesioned hemisphere and a reduction of the

amplitude of alpha oscillations in the lesioned hemisphere, resulting in an interhemispheric imbalance of the alpha oscillatory activity. In contrast, no significant alterations were found in patients with anterior lesions. The presence of an impairment of alpha oscillatory activity after a posterior lesion, but not after an anterior lesion, suggests that posterior cortices might have a central role in coordinating alpha oscillations through the visual system. This finding is in line with the notion of posterior cortices as one of the main source of alpha oscillatory activity, coordinating and propagating alpha oscillations in the entire visual system from lower to higher-order visual areas (Bollimunta et al., 2008; Hindriks et al., 2015). Crucially, the alpha oscillatory activity recorded during the resting-state well predicted the visuospatial performance across all participants and the visual detection impairments in hemianopic patients, therefore supporting the idea of spontaneous alpha oscillatory activity as an electrophysiological correlate for the functionality of the visual system (Dugué et al., 2011; Romei et al., 2008a; Hindriks et al., 2015; Cecere, Rees, and Romei, 2015; Samaha and Postle, 2015; Wutz et al., 2018; Wutz et al., 2016; Klimesch, 1997; Klimesch, 1999; Mathewson et al., 2009). Moreover, right posterior lesions caused a greater interhemispheric imbalance in the oscillatory alpha activity, suggesting that lesions to the right posterior cortices have a more severe impact on alpha oscillatory activity. This finding is in line with prominent theories about the dominance of the right hemisphere over the left hemisphere in spatial representation (Heilman and Van Den Abell, 1980) and in balancing the interhemispheric inhibition (Kinsbourne, 1977). Consequently, the dominant role of the right hemisphere in coordinating and propagating the spontaneous alpha oscillatory activity found in the current study might reflect the dominant role of the right hemisphere in the representation of space.

Although the results of the first study revealed alterations of spontaneous alpha parameters after posterior brain lesions, they did not provide any evidence about the integrated oscillatory activity in different and spatially separated brain regions. Indeed, a coherent visual representation of the entire space need the complex integration between the top-down spatial attentional networks and the bottom-up visual processing networks (Desimone and Duncan, 1995; Treue and Maunsell, 1996). Therefore, the study of the functional connectivity during the resting-state might represent a reliable tool for testing the information flow within widespread neural networks (Westlake et al., 2012; Greicius et al., 2003). In line, in the study presented in chapter 3, in which EEG oscillatory activity was recorded during eyes-closed

resting state and functional connectivity was measured, patients with a posterior lesion showed alterations of alpha functional connectivity only in the posterior right hemisphere. Specifically, the right hemisphere showed reduced connectivity when lesioned (i.e., in hemianopic patients with right lesions) and increased connectivity when intact (i.e., in hemianopic patients with left lesions). In line with the study presented in chapter 2, this finding corroborate the idea that posterior regions might have a central role in coordinating and propagating alpha oscillations through the visual system, and further suggests a prominent role of the right hemisphere in control the information flow within the functional networks of the visual system. Moreover, patients with a posterior right lesion showed also an increased theta functional connectivity in the right-lesioned hemisphere, suggesting the presence of an additional dysfunction in the oscillatory connectivity pattern after a posterior lesion. This further corroborates the idea of a dominance of the right hemisphere in the visuospatial processing (Heilman and Van Den Abell, 1980; Kinsbourne, 1977) and the role of alpha oscillatory activity in coordinating also the activity in different frequency bands (Hindriks et al., 2015). Crucially, the alterations of alpha functional connectivity were directly linked to the visuospatial performance across all participants, in line with the findings reported in chapter 2 and corroborating the hypothesis that alpha dynamics at rest might reflect an index of the efficiency of the visual processing.

Overall the findings of the studies in chapters 2 and 3 demonstrated that patients with a posterior lesion showed a consistent impairment in the spontaneous alpha oscillatory activity, reflecting an impairment in the functionality of the visual system. However, these results do not reveal if the observed spontaneous alpha oscillatory activity reflects impaired but functional neural processing or only residual activity without any functional role. In the study in the chapter 4, the functionality of the spontaneous alpha oscillatory activity was investigated after a posterior lesion by the study of the typical alpha suppression found for the transition from the eyes-closed to the eyes-open resting-state (Ben-Simon et al., 2008; Barry et al., 2007). The results revealed that, similarly to healthy participants, hemianopic patients showed the presence of a suppression of the alpha oscillatory activity in the transition from eyes-closed to eyes-open resting-state. However, alpha suppression in hemianopic patients was reduced compared to the reactivity of alpha oscillatory activity in the healthy participants. These findings suggest that after posterior lesions, although activity in the alpha range is

altered and reduced, residual alpha oscillatory activity is not fully impaired, therefore suggesting some sparing of the functionality of the visual system. Moreover, right posterior lesions also altered the reactivity pattern of theta oscillatory activity. Specifically, an increase in theta power at the opening of the eyes was found in right-lesioned hemianopic patients, whereas theta amplitude showed a typical decrease in all the other groups. Accordingly, the typical suppression of theta oscillatory activity at the opening of the eyes has been generally associated with local cortical activation underlying visual processing. Thus, the lack of theta suppression in hemianopic patients with right lesions suggests that damage to right posterior cortices are more detrimental for visual reactivity (Barry et al., 2007). In line, previous studies have proposed that alpha oscillatory activity might reflect the activity of widespread cortical networks, regulating the local processing in non-alpha frequency bands (Doesburg et al., 2009; Barry and De Blasio, 2017). Consequently, the altered theta oscillatory activity found in the studies in the chapter 3 and 4 suggests that the impairment of the alpha oscillatory activity after a right posterior lesion might also induce an impairment of local processing in lower frequency bands. Therefore, these converging findings suggest a central role of the right posterior cortices in coordinating and propagating the spontaneous alpha oscillatory activity and in regulating the spontaneous lower frequency oscillatory activity, possibly reflecting the central role of the right hemisphere in shaping a coherent visual representation of the entire space.

The results from the studies in chapters 2, 3 and 4 suggested that some degree of functionality of the spontaneous alpha oscillatory activity is spared after a posterior brain lesion, probably reflecting the presence of a residual functionality of the visual system after a posterior lesion. Indeed, posterior brain lesions usually spare subcortical and cortical structures which might sustain residual visual processing (Tamietto and Morrone, 2016; Tamietto et al., 2012). For instance, the SC is a pivotal subcortical structure which has been demonstrated to be involved in mediating implicit visual processing in the absence of awareness after posterior brain lesions (Tamietto et al., 2010; Spering and Carrasco, 2015; Rodman et al., 1989; 1990; Girard et al., 1992; Azzopardi et al., 2003; Tran et al., 2019; Tamietto et al., 2012; Rafal et al., 2015) and is typically intact after cortical lesions inducing visual field defects. In addition, the SC has also a prominent role in programming and generating eye-movements (Munoz and Wurtz, 1995a; 1995b; Krauzlis et al., 2013). In this perspective, the study in chapter 5 investigated

whether patients with posterior lesions might retain the ability of implicitly processing stimuli in the blind field, using a saccadic localization task. The results showed that left-lesioned hemianopic patients, but not right-lesioned hemianopic patients, showed a delay in the initiation of saccades toward targets presented in the intact field when a concurrent distractor was presented in the blind field. The interference of the unseen distractor on the saccadic response toward a seen target suggests that hemianopic patients can process unseen visual stimuli presented in their blind field in the absence of awareness. Classical studies on patient with visual field defects with blindsight have reported residual abilities to discriminate above the chance level the presence, the features or the location of visual stimuli presented in the blind field in forced choice tasks (Blythe et al., 1987; Perenin and Jeannerod, 1975; Weiskrantz et al., 1974; Pöppel et al., 1973). However, blindsight seems to represent a rare neuropsychological condition which might arise from a peculiar reorganization of the visual system. Indeed, hemianopic patients usually do not show above chance level discriminative abilities for visual stimuli presented in the blind field. Nevertheless, the present findings demonstrate that also hemianopic patients without blindsight can process some categories of stimuli in their blind visual field. This is in line with the recent findings on hemianopic patients without blindsight showing the presence of residual visual processing for very specific categories of stimuli, i.e. motion stimuli and fearful faces, presented in the blind visual field (Grasso et al., 2018; Bertini et al., 2013; Bertini et al., 2018; Bertini et al., 2017; Cecere et al., 2014). These implicit visual abilities, which seems selective for certain stimuli, has been attributed to the involvement of the visual pathways conveying visual information from the retina, to the SC and then projecting to subcortical and cortical structures, relevant in processing these specific categories of stimuli (Bertini et al., 2013; Bertini et al., 2018; Bertini et al., 2017). The same pathway might subserve also the saccadic interference effect with unseen stimuli observed in the present study. Indeed, in healthy participants the interference of a distractor presented in one hemifield on the saccadic response toward target presented in the other hemifield has been attributed to inhibitory mechanisms within the SC (Findlay and Walker, 1999; Walker et al., 1997; Gandhi and Keller, 1999) and the interplay between the SC and the higher-order cortical region for the control of eye-movements FEF (Dorris et al., 2007; Sommer and Wurtz 2004a; 2004b). These evidences suggest that the residual visual processing observed in chapter 5 might be mediated by the SC and the

interplay between the SC and the FEF. The presence of a residual visual processing only in left-lesioned patients is in line with the literature about the cortical asymmetry in the representation of space, in which the right hemisphere shows a dominant role compared to the left hemisphere (Heilman and Van Den Abell, 1980; Kinsbourne, 1977; Corbetta and Shulman, 2002; 2011; Duecker and Sack, 2015). Indeed, the FEF, a cortical region that contribute together with the SC to the programming of saccades, shows in several studies a strong asymmetry in visuospatial abilities, where the right FEF is able to represent both the contra- and ipsi-lateral hemifields and, on contrary, the left FEF is able to represent only the contralateral hemifield (Grosbras and Paus, 2003; Chanes et al., 2012; Duecker et al., 2013; Duecker and Sack, 2015).

In conclusion, in the present work the functionality of the visual system has been investigated after lesions of posterior visual cortices. Evidence demonstrating the presence of visual processing in the absence of awareness in hemianopic patients without blindsight has been provided, suggesting that subcortical structures spared after lesions inducing visual field defects might mediate implicit visual abilities. Moreover, electrophysiological evidence have been also provided, corroborating the notion that spontaneous alpha oscillatory activity might be a reliable biomarker for the functionality of the visual system, opening up the future possibility to predict the visuospatial impairment of hemianopic patients before the use of any behavioral test. More importantly, the tight relationship between alpha oscillatory activity and the functionality of the visual system suggests that active modulation of alpha oscillatory activity might ameliorate the functionality of the visual system in patients with visual field defect. Accordingly, in healthy participants it has been reported that both oscillatory activity and visual performance can be temporarily enhanced by a rhythmic transcranial magnetic stimulation at alpha frequency (Thut et al., 2011; Romei, Gross, and Thut, 2010), by a flickering visual stimulation at alpha frequency (Mathewson, Prudhomme, Fabiani, Beck, Lleras, and Gratton, 2012; de Graaf, Gross, Paterson, Rusch, Sack, and Thut, 2013) and by training individuals to alter their brain activity oscillatory activity via neurofeedback (Twemlow and Bowen, 1977; Angelakis, Stathopoulou, Frymiare, Green, Lubar, and Kounios, 2007). Therefore, future studies should focus on the development of stimulation protocols able to induce long term plastic changes in the impaired alpha oscillatory activity

after a posterior lesion, in order to improve the spared functionality of the visual system of hemianopic patients.

Reference

Aertsen, A., G. Gerstein, M. Habib, and G. Palm. 1989. “Dynamics of Neuronal Firing Correlation: Modulation of ‘Effective Connectivity.’” *Journal of Neurophysiology* 61 (5): 900–917. https://doi.org/10.1152/jn.1989.61.5.900.

Ajina, S., C. Kennard, G. Rees, and H. Bridge. 2014. “Motion Area V5/MT+ Response to Global Motion in the Absence of V1 Resembles Early Visual Cortex.” *Brain* 138 (1): 164–178.

Alberti, C., E. Peli, and A. Bowers. 2014. “Driving with Hemianopia: III. Detection of Stationary and Approaching Pedestrians in a Simulator.” *Investigative Ophthalmology & Visual Science* 55 (1): 368–74. https://doi.org/10.1167/iovs.13-12737.

Albright, T. 1984. “Direction and Orientation Selectivity of Neurons in Visual Area MT of the Macaque.” *Journal of Neurophysiology* 52 (6): 1106–30. https://doi.org/10.1152/jn.1984.52.6.1106.

Allen, E., E. Damaraju, T. Eichele, L. Wu, and V. Calhoun. 2018. “EEG Signatures of Dynamic Functional Network Connectivity States.” *Brain Topography* 31 (1): 101–16. https://doi.org/10.1007/s10548-017-0546-2.

Anders, S., N. Birbaumer, B. Sadowski, M. Erb, I. Mader, W. Grodd, and M. Lotze. 2004. “Parietal Somatosensory Association Cortex Mediates Affective Blindsight.” *Nature Neuroscience* 7 (4): 339–40. https://doi.org/10.1038/nn1213.

Anders, S., F. Eippert, S. Wiens, N. Birbaumer, M. Lotze, and D. Wildgruber. 2009. “When Seeing Outweighs Feeling: A Role for Prefrontal Cortex in Passive Control of Negative Affect in Blindsight.” *Brain: A Journal of Neurology* 132 (Pt 11): 3021–31. https://doi.org/10.1093/brain/awp212.

Angelakis, E., S. Stathopoulou, J. Frymiare, D. Green, J. Lubar, and J. Kounios. 2007. “EEG Neurofeedback: A Brief Overview and an Example of Peak Alpha Frequency Training for Cognitive Enhancement in the Elderly.” *The Clinical Neuropsychologist* 21 (1): 110–29. https://doi.org/10.1080/13854040600744839.

Azzopardi, P., M. Fallah, C. Gross, and H. Rodman. 2003. “Response Latencies of Neurons in Visual Areas MT and MST of Monkeys with Striate Cortex Lesions.”

Neuropsychologia, The Neuropsychology of Motion Perception, 41 (13): 1738–56. https://doi.org/10.1016/S0028-3932(03)00176-3.

Babiloni, C., G. Frisoni, M. Pievani, L. Toscano, C. Del Percio, C. Geroldi, F. Eusebi, C. Miniussi, and P. Rossini. 2008. "White-Matter Vascular Lesions Correlate with Alpha EEG Sources in Mild Cognitive Impairment." *Neuropsychologia*, Neuroimaging of Early Alzheimer's Disease, 46 (6): 1707–20. https://doi.org/10.1016/j.neuropsychologia.2008.03.021.

Babiloni, C., R. Lizio, N. Marzano, P. Capotosto, A. Soricelli, A. Triggiani, S. Cordone, L. Gesualdo, and C. Del Percio. 2016. "Brain Neural Synchronization and Functional Coupling in Alzheimer's Disease as Revealed by Resting State EEG Rhythms." *International Journal of Psychophysiology*, Research on Brain Oscillations and Connectivity in A New Take-Off State, 103 (May): 88–102. https://doi.org/10.1016/j.ijpsycho.2015.02.008.

Barry, R., and F. De Blasio. 2017. "EEG Differences between Eyes-Closed and Eyes-Open Resting Remain in Healthy Ageing." *Biological Psychology* 129 (April): 293–304. https://doi.org/10.1016/j.biopsycho.2017.09.010.

Barry, R., A. Clarke, S. Johnstone, and C. Brown. 2009. "Clinical Neurophysiology EEG Differences in Children between Eyes-Closed and Eyes-Open Resting Conditions." *Clinical Neurophysiology* 120 (10): 1806–11. https://doi.org/10.1016/j.clinph.2009.08.006.

Barry, R., A. Clarke, S. Johnstone, C. Magee, and J. Rushby. 2007. "EEG Differences between Eyes-Closed and Eyes-Open Resting Conditions." *Clinical Neurophysiology* 118 (12): 2765–73. https://doi.org/10.1016/j.clinph.2007.07.028.

Barton, J., M. Behrmann, and S. Black. 1998. "Ocular Search during Line Bisection. The Effects of Hemi-Neglect and Hemianopia." *Brain: A Journal of Neurology* 121 (6): 1117–1131.

Başar, E. 1999. *Brain Function and Oscillations: Volume II: Integrative Brain Function. Neurophysiology and Cognitive Processes*. Springer Series in Synergetics. Berlin Heidelberg: Springer-Verlag. https://doi.org/10.1007/978-3-642-59893-7.

Bastos, A., and J. Schoffelen. 2016. “A Tutorial Review of Functional Connectivity Analysis Methods and Their Interpretational Pitfalls.” *Frontiers in Systems Neuroscience* 9. https://doi.org/10.3389/fnsys.2015.00175.

Bazanova, O., and D. Vernon. 2014. “Neuroscience and Biobehavioral Reviews Interpreting EEG Alpha Activity.” *Neuroscience and Biobehavioral Reviews* 44: 94–110. https://doi.org/10.1016/j.neubiorev.2013.05.007.

Ben-Simon, E., I. Podlipsky, A. Arieli, A. Zhdanov, and T. Hendler. 2008. “Never Resting Brain: Simultaneous Representation of Two Alpha Related Processes in Humans.” *PLOS ONE* 3 (12): e3984. https://doi.org/10.1371/journal.pone.0003984.

Ben-Simon, E., I. Podlipsky, H. Okon-singer, M. Gruberger, D. Cvetkovic, N. Intrator, and T. Hendler. 2013. “The Dark Side of the Alpha Rhythm : FMRI Evidence for Induced Alpha Modulation during Complete Darkness” 37 (April 2012): 795–803. https://doi.org/10.1111/ejn.12083.

Benwell, C., R. London, C. Tagliabue, D. Veniero, J. Gross, C. Keitel, and G. Thut. 2019. “Frequency and Power of Human Alpha Oscillations Drift Systematically with Time-on-Task.” *NeuroImage* 192 (May): 101–14. https://doi.org/10.1016/j.neuroimage.2019.02.067.

Benwell, C., C. Tagliabue, D. Veniero, R. Cecere, S. Savazzi, and G. Thut. 2017. “Prestimulus EEG Power Predicts Conscious Awareness But Not Objective Visual Performance.” *ENeuro* 4 (6). https://doi.org/10.1523/ENEURO.0182-17.2017.

Berger, H. 1929. “Uber Das Elektrenkephalogramm Des Menschen.” 278 (1875).

Bertini, C., R. Cecere, and E. Làdavas. 2013. “I Am Blind, but I ‘See’ Fear.” *Cortex* 49 (4): 985–993.

Bertini, C., R. Cecere, and E. Làdavas. 2017. “Unseen Fearful Faces Facilitate Visual Discrimination in the Intact Field.” *Neuropsychologia*.

Bertini, C., M. Pietrelli, D. Braghittoni, and E. Làdavas. 2018. “Pulvinar Lesions Disrupt Fear-Related Implicit Visual Processing in Hemianopic Patients.” *Frontiers in Psychology* 9.

Bianciardi, M., M. Fukunaga, P. van Gelderen, S. Horovitz, J. de Zwart, and J. Duyn. 2009. “Modulation of Spontaneous FMRI Activity in Human Visual Cortex by Behavioral

State." *NeuroImage* 45 (1): 160–68. https://doi.org/10.1016/j.neuroimage.2008.10.034.

Biersdorf, W., R. Bell, and R. Beck. 1992. "Pattern Flash Visual Evoked Potentials in Patients with Homonymous Hemianopia." *Documenta Ophthalmologica* 80 (1): 51–61. https://doi.org/10.1007/BF00161231.

Bisiach, E., L. Pizzamiglio, D. Nico, and G. Antonucci. 1996. "Beyond Unilateral Neglect." *Brain* 119 (3): 851–57. https://doi.org/10.1093/brain/119.3.851.

Bisiach, E., and C. Luzzatti. 1978. "Unilateral neglect of representational space". *Cortex*, 14(1), 129-133.

Blythe, I., C. Kennard, and K. Ruddock. 1987. "Residual Vision in Patients with Retrogeniculate Lesions of the Visual Pathways." *Brain* 110 (4): 887–905.

Blythe, I., J. Bromley, C. Kennard, and K. Ruddock. 1986. "Visual Discrimination of Target Displacement Remains after Damage to the Striate Cortex in Humans." *Nature* 320 (6063): 619.

Bola, M., C. Gall, C. Moewes, A. Fedorov, H. Hinrichs, and B. Sabel. 2014. "Brain Functional Connectivity Network Breakdown and Restoration in Blindness." *Neurology* 83 (6): 542–51. https://doi.org/10.1212/WNL.0000000000000672.

Bola, M., C. Gall, and B. Sabel. 2015. "Disturbed Temporal Dynamics of Brain Synchronization in Vision Loss." *Cortex* 67 (June): 134–46. https://doi.org/10.1016/j.cortex.2015.03.020.

Bollimunta, A., Y. Chen, C. Schroeder, and M. Ding. 2008. "Neuronal Mechanisms of Cortical Alpha Oscillations in Awake-Behaving Macaques." *Journal of Neuroscience* 28 (40): 9976–88. https://doi.org/10.1523/JNEUROSCI.2699-08.2008.

Bollini, A., J. Sanchez-Lopez, S. Savazzi, and C. Marzi. 2017. "Lights from the Dark: Neural Responses from a Blind Visual Hemifield." *Frontiers in Neuroscience* 11. https://doi.org/10.3389/fnins.2017.00290.

Bolognini, N., F. Rasi, M. Coccia, and E. Làdavas. 2005. "Visual Search Improvement in Hemianopic Patients after Audio-Visual Stimulation." *Brain* 128 (12): 2830–42. https://doi.org/10.1093/brain/awh656.

Bonnard, M., S. Chen, J. Gaychet, M. Carrere, M. Woodman, B. Giusiano, and V. Jirsa. 2016. “Resting State Brain Dynamics and Its Transients: A Combined TMS-EEG Study.” *Scientific Reports* 6 (August): 31220. https://doi.org/10.1038/srep31220.

Bourne, J., and M. Morrone. 2017. “Plasticity of Visual Pathways and Function in the Developing Brain: Is the Pulvinar a Crucial Player?” *Frontiers in Systems Neuroscience* 11: 3.

Boussaoud, D., L. Ungerleider, and R. Desimone. 1990. “Pathways for Motion Analysis: Cortical Connections of the Medial Superior Temporal and Fundus of the Superior Temporal Visual Areas in the Macaque.” *Journal of Comparative Neurology* 296 (3): 462–495.

Bowers, A., E. Ananyev, A. Mandel, R. Goldstein, and E. Peli. 2014. “Driving with Hemianopia: IV. Head Scanning and Detection at Intersections in a Simulator.” *Investigative Ophthalmology & Visual Science* 55 (3): 1540–48. https://doi.org/10.1167/iovs.13-12748.

Bowers, A., A. Mandel, R. Goldstein, and E. Peli. 2009. “Driving with Hemianopia, I: Detection Performance in a Driving Simulator.” *Investigative Ophthalmology & Visual Science* 50 (11): 5137–47. https://doi.org/10.1167/iovs.09-3799.

Bowers, A., M. Tant, and E. Peli. 2012. “A Pilot Evaluation of On-Road Detection Performance by Drivers with Hemianopia Using Oblique Peripheral Prisms.” *Stroke Research and Treatment* 2012: 176806. https://doi.org/10.1155/2012/176806.

Bowers, D. and K. Heilman. 1980. “Pseudoneglect: Effects of Hemispace on a Tactile Line Bisection Task.” *Neuropsychologia* 18 (4): 491–98. https://doi.org/10.1016/0028-3932(80)90151-7.

Brent, P., C. Kennard, and K. Ruddock. 1994. “Residual Colour Vision in a Human Hemianope: Spectral Responses and Colour Discrimination.” *Proceedings of the Royal Society of London. Series B: Biological Sciences* 256 (1347): 219–225.

Brigell, M., G. Celesia, F. Salvi, and R. Clark-Bash. 1990. “Topographic Mapping of Electrophysiologic Measures in Patients with Homonymous Hemianopia.” *Neurology* 40 (10): 1566–70. https://doi.org/10.1212/wnl.40.10.1566.

Brighina, F., E. Bisiach, A. Piazza, M. Oliveri, V. La Bua, O. Daniele, and B. Fierro. 2002. “Perceptual and Response Bias in Visuospatial Neglect Due to Frontal and Parietal

Repetitive Transcranial Magnetic Stimulation in Normal Subjects." *NeuroReport* 13 (18): 2571.

Burra, N., A. Hervais-Adelman, A. Celeghin, B. de Gelder, and A. Pegna. 2019. "Affective Blindsight Relies on Low Spatial Frequencies." *Neuropsychologia* 128: 44–49. https://doi.org/10.1016/j.neuropsychologia.2017.10.009.

Busch, N., J. Dubois, and R. VanRullen. 2009. "The Phase of Ongoing EEG Oscillations Predicts Visual Perception." *Journal of Neuroscience* 29 (24): 7869–76. https://doi.org/10.1523/JNEUROSCI.0113-09.2009.

Butz, M., J. Gross, L. Timmermann, M. Moll, H. Freund, O. Witte, and A. Schnitzler. 2004. "Perilesional Pathological Oscillatory Activity in the Magnetoencephalogram of Patients with Cortical Brain Lesions." *Neuroscience Letters* 355 (1): 93–96. https://doi.org/10.1016/j.neulet.2003.10.065.

Capilla, A., J. Schoffelen, G. Paterson, G. Thut, and J. Gross. 2014. "Dissociated α-Band Modulations in the Dorsal and Ventral Visual Pathways in Visuospatial Attention and Perception." *Cerebral Cortex* 24 (2): 550–61. https://doi.org/10.1093/cercor/bhs343.

Carmichael, S. and M. Chesselet. 2002. "Synchronous Neuronal Activity Is a Signal for Axonal Sprouting after Cortical Lesions in the Adult." *Journal of Neuroscience* 22 (14): 6062–70. https://doi.org/10.1523/JNEUROSCI.22-14-06062.2002.

Carpenter, R. and M. Williams. 1995. "Neural Computation of Log Likelihood in Control of Saccadic Eye Movements." *Nature* 377 (6544): 59–62. https://doi.org/10.1038/377059a0.

Castellanos, N., N. Paúl, V. Ordóñez, O. Demuynck, R. Bajo, P. Campo, A. Bilbao, T. Ortiz, F. del-Pozo, and F. Maestú. 2010. "Reorganization of Functional Connectivity as a Correlate of Cognitive Recovery in Acquired Brain Injury." *Brain* 133 (8): 2365–81. https://doi.org/10.1093/brain/awq174.

Cecere, R., C. Bertini, M. Maier, and E. Làdavas. 2014. "Unseen Fearful Faces Influence Face Encoding: Evidence from ERPs in Hemianopic Patients." *Journal of Cognitive Neuroscience* 26 (11): 2564–77. https://doi.org/10.1162/jocn_a_00671.

Cecere, R., G. Rees, and V. Romei. 2015. “Individual Differences in Alpha Frequency Drive Crossmodal Illusory Perception.” *Current Biology* 25 (2): 231–35. https://doi.org/10.1016/j.cub.2014.11.034.

Celeghin, A., A. Bagnis, M. Diano, C. Méndez, T. Costa, and M. Tamietto. 2019. “Functional Neuroanatomy of Blindsight Revealed by Activation Likelihood Estimation Meta-Analysis.” *Neuropsychologia*, Neural Routes to Awareness in Vision, Emotion and Action: A tribute to Larry Weiskrantz, 128 (May): 109–18. https://doi.org/10.1016/j.neuropsychologia.2018.06.007.

Celeghin, A., M. Diano, B. de Gelder, L. Weiskrantz, C. Marzi, and M. Tamietto. 2017. “Intact Hemisphere and Corpus Callosum Compensate for Visuomotor Functions after Early Visual Cortex Damage.” *Proceedings of the National Academy of Sciences* 114 (48): E10475–83. https://doi.org/10.1073/pnas.1714801114.

Celeghin, A., B. de Gelder, and M. Tamietto. 2015. “From Affective Blindsight to Emotional Consciousness.” *Consciousness and Cognition* 36 (November): 414–25. https://doi.org/10.1016/j.concog.2015.05.007.

Celesia, G., J. Meredith, and K. Pluff. 1983. “Perimetry, Visual Evoked Potentials and Visual Evoked Spectrum Array in Homonymous Hemianopsia.” *Electroencephalography and Clinical Neurophysiology* 56 (1): 16–30. https://doi.org/10.1016/0013-4694(83)90003-2.

Chacko, L. 1948. “The Laminar Pattern of the Lateral Geniculate Body in the Primates.” *Journal of Neurology, Neurosurgery, and Psychiatry* 11 (3): 211.

Chalupa, L. 1991. “Visual Function of the Pulvinar.” In *The Neural Basis of Visual Function*, 4:141–159. CRC Press Boca Raton.

Chanes, L., A. Chica, R. Quentin, and A. Valero-Cabré. 2012. “Manipulation of Pre-Target Activity on the Right Frontal Eye Field Enhances Conscious Visual Perception in Humans.” *PLOS ONE* 7 (5): e36232. https://doi.org/10.1371/journal.pone.0036232.

Chedru, F., M. Leblanc, and F. Lhermitte. 1973. “Visual Searching in Normal and Brain-Damaged Subjects (Contribution to the Study of Unilateral Inattention).” *Cortex* 9 (1): 94–111.

Chu, R., A. Braun, and J. Meltzer. 2015. “MEG-Based Detection and Localization of Perilesional Dysfunction in Chronic Stroke.” *NeuroImage: Clinical* 8 (January): 157–69. https://doi.org/10.1016/j.nicl.2015.03.019.

Cohen, M. 2011. “It’s about Time.” *Frontiers in Human Neuroscience* 5. https://doi.org/10.3389/fnhum.2011.00002.

Cohen, M. 2014. *Analyzing Neural Time Series Data: Theory and Practice*. MIT Press.

Colombo, C., O. Gambini, F. Macciardi, L. Bellodi, E. Sacchetti, A. Vita, R. Cattaneo, and S. Scarone. 1989. “Alpha Reactivity in Schizophrenia and in Schizophrenic Spectrum Disorders: Demographic, Clinical and Hemispheric Assessment.” *International Journal of Psychophysiology* 7 (1): 47–54. https://doi.org/10.1016/0167-8760(89)90030-5.

Corbetta, M., F. Miezin, G. Shulman, and S. Petersen. 1993. “A PET Study of Visuospatial Attention.” *Journal of Neuroscience* 13 (3): 1202–26. https://doi.org/10.1523/JNEUROSCI.13-03-01202.1993.

Corbetta, M., C. Marzi, G. Tassinari, and S. Aglioti. 1990. “Effectiveness of Different Task Paradigms in Revealing Blindsight.” *Brain* 113 (3): 603–616.

Corbetta, M. and G. Shulman. 2002. “Control of Goal-Directed and Stimulus-Driven Attention in the Brain.” *Nature Reviews Neuroscience* 3 (3): 201–15. https://doi.org/10.1038/nrn755.

Corbetta, M., and G. Shulman. 2011. “Spatial Neglect and Attention Networks.” *Annual Review of Neuroscience* 34: 569–599.

Corcoran, A., P. Alday, M. Schlesewsky, and I. Bornkessel-Schlesewsky. 2018. “Toward a Reliable, Automated Method of Individual Alpha Frequency (IAF) Quantification.” *Psychophysiology* 55 (7): e13064. https://doi.org/10.1111/psyp.13064.

Cowey, A., and P. Stoerig. 1989. “Projection Patterns of Surviving Neurons in the Dorsal Lateral Geniculate Nucleus Following Discrete Lesions of Striate Cortex: Implications for Residual Vision.” *Experimental Brain Research* 75 (3): 631–638.

Cowey, A. 2004. "The 30th Sir Frederick Bartlett lecture: Fact, artefact, and myth about blindsight." *Quarterly Journal of Experimental Psychology* Section A 57: 577-609.

Croner, L. and E. Kaplan. 1995. “Receptive Fields of P and M Ganglion Cells across the Primate Retina.” *Vision Research* 35 (1): 7–24.

Cynader, M. and N. Berman. 1972. “Receptive-Field Organization of Monkey Superior Colliculus.” *Journal of Neurophysiology* 35 (2): 187–201.

Dawson, K. 2004. “Temporal Organization of the Brain: Neurocognitive Mechanisms and Clinical Implications.” *Brain and Cognition* 54 (1): 75–94. https://doi.org/10.1016/S0278-2626(03)00262-8.

De Gelder, B., G. Pourtois, M. van Raamsdonk, J. Vroomen, and L. Weiskrantz. 2001. “Unseen Stimuli Modulate Conscious Visual Experience: Evidence from Inter-Hemispheric Summation.” *NeuroReport* 12 (2): 385.

De Gelder, B., J. Vroomen, G. Pourtois, and L. Weiskrantz. 1999. “Non-Conscious Recognition of Affect in the Absence of Striate Cortex.” *Neuroreport* 10 (18): 3759–3763.

Del Zotto, M., M. Deiber, L. Legrand, B. De Gelder, and A. Pegna. 2013. “Emotional Expressions Modulate Low α and β Oscillations in a Cortically Blind Patient.” *International Journal of Psychophysiology* 90 (3): 358–62. https://doi.org/10.1016/j.ijpsycho.2013.10.007.

Delorme, A., and S. Makeig. 2004. “EEGLAB: An Open Source Toolbox for Analysis of Single-Trial EEG Dynamics Including Independent Component Analysis.” *Journal of Neuroscience Methods* 134 (1): 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009.

Desimone, R. and J. Duncan. 1995. “Neural Mechanisms of Selective Visual Attention.” *Annual Review of Neuroscience* 18 (1): 193–222.

Diessen, E. van, T. Numan, E. van Dellen, A. van der Kooi, M. Boersma, D. Hofman, R. van Lutterveld. 2015. “Opportunities and Methodological Challenges in EEG and MEG Resting State Functional Brain Network Research.” *Clinical Neurophysiology* 126 (8): 1468–81. https://doi.org/10.1016/j.clinph.2014.11.018.

Dijk, H. van, J. Schoffelen, R. Oostenveld, and O. Jensen. 2008. “Prestimulus Oscillatory Activity in the Alpha Band Predicts Visual Discrimination Ability.” *Journal of Neuroscience* 28 (8): 1816–23. https://doi.org/10.1523/JNEUROSCI.1853-07.2008.

Ding, J., G. Sperling, and R. Srinivasan. 2006. “Attentional Modulation of SSVEP Power Depends on the Network Tagged by the Flicker Frequency.” *Cerebral Cortex (New York, N.Y.: 1991)* 16 (7): 1016–29. https://doi.org/10.1093/cercor/bhj044.

Di Russo, F., W. Teder-Sälejärvi, and S. Hillyard. 2003. “Chapter 11 - Steady-State VEP and Attentional Visual Processing.” In *the Cognitive Electrophysiology of Mind and Brain*, edited by Alberto Zani, Alice Mado Proverbio, and Michael I. Posner, 259–74. San Diego: Academic Press. https://doi.org/10.1016/B978-012775421-5/50013-3.

Doesburg, S., J. Green, J. McDonald, and L. Ward. 2009. “From Local Inhibition to Long-Range Integration: A Functional Dissociation of Alpha-Band Synchronization across Cortical Scales in Visuospatial Attention.” *Brain Research* 1303 (November): 97–110. https://doi.org/10.1016/j.brainres.2009.09.069.

Doricchi, F., A. Onida, and P. Guariglia. 2002. “Horizontal Space Misrepresentation in Unilateral Brain Damage: II. Eye-Head Centered Modulation of Visual Misrepresentation in Hemianopia without Neglect.” *Neuropsychologia* 40 (8): 1118–1128.

Dorris, M., E. Olivier, and D. Munoz. 2007. “Competitive Integration of Visual and Preparatory Signals in the Superior Colliculus during Saccadic Programming.” *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 27 (19): 5053–62. https://doi.org/10.1523/JNEUROSCI.4212-06.2007.

Dubovik, S., J. Pignat, R.Ptak, T. Aboulafia, L. Allet, N. Gillabert, and C. Magnin. 2012. “The Behavioral Significance of Coherent Resting-State Oscillations after Stroke.” *NeuroImage* 61 (1): 249–57. https://doi.org/10.1016/j.neuroimage.2012.03.024.

Duecker, F., E. Formisano, and A. Sack. 2013. “Hemispheric Differences in the Voluntary Control of Spatial Attention: Direct Evidence for a Right-Hemispheric Dominance within Frontal Cortex.” *Journal of Cognitive Neuroscience* 25 (8): 1332–42. https://doi.org/10.1162/jocn_a_00402.

Duecker, F. and A. Sack. 2015. “The Hybrid Model of Attentional Control: New Insights into Hemispheric Asymmetries Inferred from TMS Research.” *Neuropsychologia* 74: 21–29.

Duffau, H. 2017. Diffuse low-grade gliomas in adults. Springer International Publishing.

Dugué, L., P. Marque, and R. VanRullen. 2011. “The Phase of Ongoing Oscillations Mediates the Causal Relation between Brain Excitation and Visual Perception.” *Journal of Neuroscience* 31 (33): 11889–93. https://doi.org/10.1523/JNEUROSCI.1161-11.2011.

Dundon, N., C. Bertini, E. Làdavas, B. Sabel, and C. Gall. 2015. “Visual Rehabilitation: Visual Scanning, Multisensory Stimulation and Vision Restoration Trainings.” *Frontiers in Behavioral Neuroscience* 9. https://doi.org/10.3389/fnbeh.2015.00192.

Dunkley, B., L. Da Costa, A. Bethune, R. Jetly, E. Pang, M. Taylor, and S. Doesburg. 2015. “Low-Frequency Connectivity Is Associated with Mild Traumatic Brain Injury.” *NeuroImage: Clinical* 7 (January): 611–21. https://doi.org/10.1016/j.nicl.2015.02.020.

Elgin, J., G. McGwin, J. Wood, M. Vaphiades, R. Braswell, D. DeCarlo, L. Kline, and C. Owsley. 2010. “Evaluation of On-Road Driving in People with Hemianopia and Quadrantanopia.” *The American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association* 64 (2): 268–78. https://doi.org/10.5014/ajot.64.2.268.

Ergenoglu, T., T. Demiralp, Z. Bayraktaroglu, M. Ergen, H. Beydagi, and Y. Uresin. 2004. “Alpha Rhythm of the EEG Modulates Visual Detection Performance in Humans.” *Cognitive Brain Research* 20 (3): 376–83. https://doi.org/10.1016/j.cogbrainres.2004.03.009.

Ffytche, D., C. Guy, and S. Zeki. 1996. “Motion Specific Responses from a Blind Hemifield.” *Brain* 119 (6): 1971–82. https://doi.org/10.1093/brain/119.6.1971.

Fierro, B., F. Brighina, M. Oliveri, A. Piazza, V. La Bua, D. Buffa, and E. Bisiach. 2000. “Contralateral Neglect Induced by Right Posterior Parietal RTMS in Healthy Subjects.” *NeuroReport* 11 (7): 1519.

Findlay, J. and R. Walker. 1999. “A Model of Saccade Generation Based on Parallel Processing and Competitive Inhibition.” *Behavioral and Brain Sciences* 22 (4): 661–674.

Fingelkurts, A., A. Fingelkurts, H. Rytsälä, K. Suominen, E. Isometsä, and S. Kähkönen. 2007. “Impaired Functional Connectivity at EEG Alpha and Theta Frequency Bands in Major Depression.” *Human Brain Mapping* 28 (3): 247–61. https://doi.org/10.1002/hbm.20275.

Gaetano, J., 2018. "Holm-Bonferroni sequential correction: An Excel calculator (1.3)", 10.13140/RG.2.2.28346.49604

Gale, A., M. Coles, and E. Boyd. 1971. “Variation in Visual Input and the Occipital EEG: II.” *Psychonomic Science* 23 (1): 99–100. https://doi.org/10.3758/BF03336026.

Gandhi, N. and E. Keller. 1999. “Comparison of Saccades Perturbed by Stimulation of the Rostral Superior Colliculus, the Caudal Superior Colliculus, and the Omnipause Neuron Region.” *Journal of Neurophysiology* 82 (6): 3236–3253.

Garcia-Rill, E., N. Kezunovic, J. Hyde, C. Simon, P. Beck, and F. Urbano. 2013. “Coherence and Frequency in the Reticular Activating System (RAS).” *Sleep Medicine Reviews* 17 (3): 227–38. https://doi.org/10.1016/j.smrv.2012.06.002.

Gawel, M., E. Zalewska, E. Szmidt-Sałkowska, and J. Kowalski. 2009. “The Value of Quantitative EEG in Differential Diagnosis of Alzheimer’s Disease and Subcortical Vascular Dementia.” *Journal of the Neurological Sciences*, Vascular Dementia, 283 (1): 127–33. https://doi.org/10.1016/j.jns.2009.02.332.

Gennari, F. 1782. *De Peculiari Structura Cerebri Nonnullisque Ejus Morbis*. Ex Regio Typographeo.

Gerbella, M., F. Caruana, and G. Rizzolatti. 2019. “Pathways for Smiling, Disgust and Fear Recognition in Blindsight Patients.” *Neuropsychologia* 128: 6–13. https://doi.org/10.1016/j.neuropsychologia.2017.08.028.

Gevins, A., M. Smith, L. McEvoy, and D. Yu. 1997. “High-Resolution EEG Mapping of Cortical Activation Related to Working Memory: Effects of Task Difficulty, Type of Processing, and Practice.” *Cerebral Cortex* 7 (4): 374–85. https://doi.org/10.1093/cercor/7.4.374.

Girard, P., P. Salin, and J. Bullier. 1992. “Response Selectivity of Neurons in Area MT of the Macaque Monkey during Reversible Inactivation of Area V1.” *Journal of Neurophysiology* 67 (6): 1437–46. https://doi.org/10.1152/jn.1992.67.6.1437.

Gitelman, D., A. Nobre, T. Parrish, K. LaBar, Y. Kim, J. Meyer, and M. Mesulam. 1999. “A Large-Scale Distributed Network for Covert Spatial Attention Further Anatomical Delineation Based on Stringent Behavioural and Cognitive Controls.” *Brain* 122 (6): 1093–1106. https://doi.org/10.1093/brain/122.6.1093.

Goodale, M., A. Milner, L. Jakobson, and D. Carey. 1991. “A Neurological Dissociation between Perceiving Objects and Grasping Them.” *Nature* 349 (6305): 154–56. https://doi.org/10.1038/349154a0.

Goodwin, D. 2014. “Homonymous Hemianopia: Challenges and Solutions.” *Clinical Ophthalmology (Auckland, N.Z.)* 8 (September): 1919–27. https://doi.org/10.2147/OPTH.S59452.

Graaf, T. de, J. Gross, G. Paterson, T. Rusch, A. Sack, and G. Thut. 2013. “Alpha-Band Rhythms in Visual Task Performance: Phase-Locking by Rhythmic Sensory Stimulation.” *PLOS ONE* 8 (3): e60035. https://doi.org/10.1371/journal.pone.0060035.

Grasso, P., E. Làdavas, and C. Bertini. 2016. “Compensatory Recovery after Multisensory Stimulation in Hemianopic Patients: Behavioral and Neurophysiological Components.” *Frontiers in Systems Neuroscience* 10. https://doi.org/10.3389/fnsys.2016.00045.

Grasso, P., M. Pietrelli, M. Zanon, E. Làdavas, and C. Bertini. 2018. “Alpha Oscillations Reveal Implicit Visual Processing of Motion in Hemianopia.” *Cortex*.

Greicius, M., B. Krasnow, A. Reiss, and V. Menon. 2003. “Functional Connectivity in the Resting Brain: A Network Analysis of the Default Mode Hypothesis.” *Proceedings of the National Academy of Sciences* 100 (1): 253–58. https://doi.org/10.1073/pnas.0135058100.

Grillon, C. and M. Buchsbaum. 1986. “Computed EEG Topography of Response to Visual and Auditory Stimuli.” *Electroencephalography and Clinical Neurophysiology* 63 (1): 42–53. https://doi.org/10.1016/0013-4694(86)90061-1.

Grosbras, M., and T. Paus. 2002. “Transcranial Magnetic Stimulation of the Human Frontal Eye Field: Effects on Visual Perception and Attention.” *Journal of Cognitive Neuroscience* 14 (7): 1109–20. https://doi.org/10.1162/089892902320474553.

Grosbras, M., and T. Paus. 2003. “Transcranial Magnetic Stimulation of the Human Frontal Eye Field Facilitates Visual Awareness.” *European Journal of Neuroscience* 18 (11): 3121–26. https://doi.org/10.1111/j.1460-9568.2003.03055.x.

Guggisberg, A., S. Honma, A. Findlay, S. Dalal, H. Kirsch, M. Berger, and S. Nagarajan. 2008. “Mapping Functional Connectivity in Patients with Brain Lesions.” *Annals of Neurology* 63 (2): 193–203. https://doi.org/10.1002/ana.21224.

Guo, X., Z. Jin, X. Feng, and S. Tong. 2014. “Enhanced Effective Connectivity in Mild Occipital Stroke Patients With Hemianopia.” *IEEE Transactions on Neural Systems*

and Rehabilitation Engineering 22 (6): 1210–17. https://doi.org/10.1109/TNSRE.2014.2325601.

Haan, G. de, J. Heutink, B. Melis-Dankers, W. Brouwer, and O. Tucha. 2015. "Difficulties in Daily Life Reported by Patients with Homonymous Visual Field Defects." *Journal of Neuro-Ophthalmology* 35 (3): 259–264.

Haig, A., E. Gordon, V. De Pascalis, R. Meares, H. Bahramali, and A. Harris. 2000. "Gamma Activity in Schizophrenia: Evidence of Impaired Network Binding?" *Clinical Neurophysiology* 111 (8): 1461–68. https://doi.org/10.1016/S1388-2457(00)00347-3.

Halligan, P., G. Fink, J. Marshall, and G. Vallar. 2003. "Spatial Cognition: Evidence from Visual Neglect." *Trends in Cognitive Sciences* 7 (3): 125–33. https://doi.org/10.1016/S1364-6613(03)00032-9.

Hamm, A., A. Weike, H. Schupp, T. Treig, A. Dressel, and C. Kessler. 2003. "Affective Blindsight: Intact Fear Conditioning to a Visual Cue in a Cortically Blind Patient." *Brain* 126 (2): 267–75. https://doi.org/10.1093/brain/awg037.

Hanslmayr, S., A. Aslan, T. Staudigl, W. Klimesch, C. Herrmann, and K. Bäuml. 2007. "Prestimulus Oscillations Predict Visual Perception Performance between and within Subjects." *NeuroImage* 37 (4): 1465–73. https://doi.org/10.1016/j.neuroimage.2007.07.011.

Härdle, W., T. Gasser, and P. Bächer. 1984. "EEG-Responsiveness to Eye Opening and Closing in Mildly Retarded Children Compared to a Control Group." *Biological Psychology* 18 (3): 185–99. https://doi.org/10.1016/0301-0511(84)90002-4.

Hardmeier, M., F. Hatz, H. Bousleiman, C. Schindler, C. Stam, and P. Fuhr. 2014. "Reproducibility of Functional Connectivity and Graph Measures Based on the Phase Lag Index (PLI) and Weighted Phase Lag Index (WPLI) Derived from High Resolution EEG." *PLOS ONE* 9 (10): e108648. https://doi.org/10.1371/journal.pone.0108648.

Hari, R., and R. Salmelin. 1997. "Human Cortical Oscillations: A Neuromagnetic View through the Skull." *Trends in Neurosciences* 20 (1): 44–49. https://doi.org/10.1016/S0166-2236(96)10065-5.

Hattar, S., H. Liao, M. Takao, D. Berson, and K. Yau. 2002. “Melanopsin-Containing Retinal Ganglion Cells: Architecture, Projections, and Intrinsic Photosensitivity.” *Science* 295 (5557): 1065–1070.

Heilman, K. and E. Valenstein. 1979. “Mechanisms Underlying Hemispatial Neglect.” *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* 5 (2): 166–170.

Heilman, K., and T. Van Den Abell. 1980. “Right Hemisphere Dominance for Attention: The Mechanism Underlying Hemispheric Asymmetries of Inattention (Neglect).” *Neurology* 30 (3): 327–327.

Heilman, K., E. Valenstein, and R. Watson. 1984 "Neglect and related disorders." *Seminars in Neurology*. Vol. 4. No. 02. by Thieme Medical Publishers, Inc., 1984.

Hendry, S. and T. Yoshioka. 1994. “A Neurochemically Distinct Third Channel in the Macaque Dorsal Lateral Geniculate Nucleus.” *Science* 264 (5158): 575–577.

Hiele, K. van der, E. Bollen, A. Vein, R. Reijntjes, R. Westendorp, M. van Buchem, H. Middelkoop, and J. van Dijk. 2008. “EEG Markers of Future Cognitive Performance in the Elderly.” *Journal of Clinical Neurophysiology* 25 (2): 83. https://doi.org/10.1097/WNP.0b013e31816a5b25.

Hindriks, R., M. Woolrich, H. Luckhoo, M. Joensson, H. Mohseni, M. Kringelbach, and G. Deco. 2015. “Role of White-Matter Pathways in Coordinating Alpha Oscillations in Resting Visual Cortex.” *NeuroImage* 106 (February): 328–39. https://doi.org/10.1016/j.neuroimage.2014.10.057.

Hirsch, J. and C. Curcio. 1989. “The Spatial Resolution Capacity of Human Foveal Retina.” *Vision Research* 29 (9): 1095–1101.

Holm, S. 1979. “A Simple Sequentially Rejective Multiple Test Procedure.” *Scandinavian Journal of Statistics* 6 (2): 65–70.

Honda, H. 2005. “The Remote Distractor Effect of Saccade Latencies in Fixation-Offset and Overlap Conditions.” *Vision Research* 45 (21): 2773–79. https://doi.org/10.1016/j.visres.2004.06.026.

Howseman, A., S. Zeki, and M. Mesulam. 1999. “Spatial Attention and Neglect: Parietal, Frontal and Cingulate Contributions to the Mental Representation and Attentional Targeting of Salient Extrapersonal Events.” *Philosophical Transactions of the Royal*

Society of London. Series B: Biological Sciences 354 (1387): 1325–46. https://doi.org/10.1098/rstb.1999.0482.

Hubel, D. and T. Wiesel. 1962. "Receptive Fields, Binocular Interaction and Functional Architecture in the Cat's Visual Cortex." *The Journal of Physiology* 160 (1): 106–154.

Hüfner, K., T. Stephan, V. Flanagin, A. Deutschländer, A. Stein, R. Kalla, T. Dera. 2009. "Differential Effects of Eyes Open or Closed in Darkness on Brain Activation Patterns in Blind Subjects." *Neuroscience Letters* 466 (1): 30–34. https://doi.org/10.1016/j.neulet.2009.09.010.

Huk, A. and D. Heeger. 2002. "Pattern-Motion Responses in Human Visual Cortex." *Nature Neuroscience* 5 (1): 72–75. https://doi.org/10.1038/nn774.

Hung, J., J. Driver, and V. Walsh. 2005. "Visual Selection and Posterior Parietal Cortex: Effects of Repetitive Transcranial Magnetic Stimulation on Partial Report Analyzed by Bundesen's Theory of Visual Attention." *Journal of Neuroscience* 25 (42): 9602–12. https://doi.org/10.1523/JNEUROSCI.0879-05.2005.

Hung, J., J. Driver, and V. Walsh. 2011. "Visual Selection and the Human Frontal Eye Fields: Effects of Frontal Transcranial Magnetic Stimulation on Partial Report Analyzed by Bundesen's Theory of Visual Attention." *Journal of Neuroscience* 31 (44): 15904–13. https://doi.org/10.1523/JNEUROSCI.2626-11.2011.

Iemi, L. and N. Busch. 2018. "Moment-to-Moment Fluctuations in Neuronal Excitability Bias Subjective Perception Rather than Strategic Decision-Making." *ENeuro* 5 (3). https://doi.org/10.1523/ENEURO.0430-17.2018.

Iramina, K., S. Ueno, and S. Matsuoka. 1996. "MEG and EEG Topography of Frontal Midline Theta Rhythm and Source Localization." *Brain Topography* 8 (3): 329–31. https://doi.org/10.1007/BF01184793.

Ishiai, S., T. Furukawa, and H. Tsukagoshi. 1987. "Eye-Fixation Patterns in Homonymous Hemianopia and Unilateral Spatial Neglect." *Neuropsychologia* 25 (4): 675–679.

Ishii, R., K. Shinosaki, S. Ukai, T. Inouye, T. Ishihara, T. Yoshimine, N. Hirabuki. 1999. "Medial Prefrontal Cortex Generates Frontal Midline Theta Rhythm." *NeuroReport* 10 (4): 675.

Jao, T., P. Vértes, A. Alexander-Bloch, I. Tang, Y. Yu, J. Chen, and E. Bullmore. 2013. "Volitional Eyes Opening Perturbs Brain Dynamics and Functional Connectivity Regardless of Light Input." *NeuroImage* 69 (April): 21–34. https://doi.org/10.1016/j.neuroimage.2012.12.007.

Jensen, O. and A. Mazaheri. 2010. "Shaping Functional Architecture by Oscillatory Alpha Activity: Gating by Inhibition." *Frontiers in Human Neuroscience* 4. https://doi.org/10.3389/fnhum.2010.00186.

Jewell, G. and M. McCourt. 2000. "Pseudoneglect: A Review and Meta-Analysis of Performance Factors in Line Bisection Tasks." *Neuropsychologia* 38 (1): 93–110. https://doi.org/10.1016/S0028-3932(99)00045-7.

Kaplan, E. and R. Shapley. 1986. "The Primate Retina Contains Two Types of Ganglion Cells, with High and Low Contrast Sensitivity." *Proceedings of the National Academy of Sciences* 83 (8): 2755–2757.

Kavcic, V., R. Triplett, A. Das, T. Martin, and K. Huxlin. 2015. "Role of Inter-Hemispheric Transfer in Generating Visual Evoked Potentials in V1-Damaged Brain Hemispheres." *Neuropsychologia* 68 (February): 82–93. https://doi.org/10.1016/j.neuropsychologia.2015.01.003.

Kayser, J. and C. Tenke. 2015. "On the Benefits of Using Surface Laplacian (Current Source Density) Methodology in Electrophysiology." *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology* 97 (3): 171–73. https://doi.org/10.1016/j.ijpsycho.2015.06.001.

Kedar, S., X. Zhang, M. Lynn, N. Newman, and V. Biousse. 2006. "Pediatric Homonymous Hemianopia." *Journal of AAPOS: The Official Publication of the American Association for Pediatric Ophthalmology and Strabismus* 10 (3): 249–52. https://doi.org/10.1016/j.jaapos.2006.01.181.

Kerkhoff, G. 2000. "Neurovisual Rehabilitation: Recent Developments and Future Directions." *Journal of Neurology, Neurosurgery, and Psychiatry* 68 (6): 691–706. https://doi.org/10.1136/jnnp.68.6.691.

Kinsbourne, M. 1977. "Hemi-Neglect and Hemisphere Rivalry." *Advances in Neurology* 18: 41–49.

Kinsbourne, M. 1987. “Mechanisms of Unilateral Neglect.” In *Advances in Psychology*, 45:69–86. Elsevier.

Klimesch, W. 1997. “EEG-Alpha Rhythms and Memory Processes.” *International Journal of Psychophysiology* 26 (1): 319–40. https://doi.org/10.1016/S0167-8760(97)00773-3.

Klimesch, W. 1999. “EEG Alpha and Theta Oscillations Reflect Cognitive and Memory Performance: A Review and Analysis.” *Brain Research Reviews* 29 (2): 169–95. https://doi.org/10.1016/S0165-0173(98)00056-3.

Klimesch, W., P. Sauseng, and S. Hanslmayr. 2007. “EEG Alpha Oscillations: The Inhibition–Timing Hypothesis.” *Brain Research Reviews* 53 (1): 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003.

Korogi, Y., M. Takahashi, T. Hirai, I. Ikushima, M. Kitajima, T. Sugahara, Y. Shigematsu, T. Okajima, and K. Mukuno. 1997. “Representation of the Visual Field in the Striate Cortex: Comparison of MR Findings with Visual Field Deficits in Organic Mercury Poisoning (Minamata Disease).” *AJNR. American Journal of Neuroradiology* 18 (6): 1127–30.

Krauzlis, R., L. Lovejoy, and A. Zénon. 2013. “Superior Colliculus and Visual Spatial Attention.” *Annual Review of Neuroscience* 36 (July): 165–82. https://doi.org/10.1146/annurev-neuro-062012-170249.

Kupfer, C. 1962. “The Projection of the Macula in the Lateral Geniculate Nucleus of Man.” *American Journal of Ophthalmology* 54 (4): 597–609.

Laaksonen, K., L. Helle, L. Parkkonen, E. Kirveskari, J. Mäkelä, S. Mustanoja, T. Tatlisumak, M. Kaste, and N. Forss. 2013. “Alterations in Spontaneous Brain Oscillations during Stroke Recovery.” *PLOS ONE* 8 (4): e61146. https://doi.org/10.1371/journal.pone.0061146.

Ledoux, J. 1998. *The Emotional Brain: The Mysterious Underpinnings of Emotional Life*. Simon and Schuster.

Leventhal, A., R. Rodieck, and B. Dreher. 1981. “Retinal Ganglion Cell Classes in the Old World Monkey: Morphology and Central Projections.” *Science* 213 (4512): 1139–1142.

Limbach, K. and P. Corballis. 2016. “Prestimulus Alpha Power Influences Response Criterion in a Detection Task.” *Psychophysiology* 53 (8): 1154–64. https://doi.org/10.1111/psyp.12666.

Liu, G. and S. Galetta. 1997. “Homonymous Hemifield Loss in Childhood.” *Neurology* 49 (6): 1748–49. https://doi.org/10.1212/wnl.49.6.1748.

Liversedge, S., I. Gilchrist, and S. Everling. 2011. *The Oxford Handbook of Eye Movements*. OUP Oxford.

Livingstone, M. and D. Hubel. 1988. “Segregation of Form, Color, Movement, and Depth: Anatomy, Physiology, and Perception.” *Science* 240 (4853): 740–749.

Ludwig, C., I. Gilchrist, and E. McSorley. 2004. “The Influence of Spatial Frequency and Contrast on Saccade Latencies.” *Vision Research* 44 (22): 2597–2604. https://doi.org/10.1016/j.visres.2004.05.022.

Ludwig, C., I. Gilchrist, and E. McSorley. 2005. “The Remote Distractor Effect in Saccade Programming: Channel Interactions and Lateral Inhibition.” *Vision Research* 45 (9): 1177–1190.

Machner, B., A. Sprenger, U. Hansen, W. Heide, and C. Helmchen. 2009. “Acute Hemianopic Patients Do Not Show a Contralesional Deviation in the Line Bisection Task.” *Journal of Neurology* 256 (2): 289–290.

Magnussen, S. and T. Mathiesen. 1989. “Detection of Moving and Stationary Gratings in the Absence of Striate Cortex.” *Neuropsychologia* 27 (5): 725–728.

Manshanden, I., J. De Munck, N. Simon, and F. da Silva. 2002. “Source Localization of MEG Sleep Spindles and the Relation to Sources of Alpha Band Rhythms.” *Clinical Neurophysiology* 113 (12): 1937–47. https://doi.org/10.1016/S1388-2457(02)00304-8.

Marcel, A. 1998. “Blindsight and Shape Perception: Deficit of Visual Consciousness or of Visual Function?” *Brain: A Journal of Neurology* 121 (8): 1565–1588.

Mariotte, E., J. Pecquet, and R. Justel. 1668. “A New Discovery Touching Vision.” *Philosophical Transactions of the Royal Society of London* 3 (35): 668–71. https://doi.org/10.1098/rstl.1668.0015.

Marx, E., T. Stephan, A. Nolte, A. Deutschländer, K. Seelos, M. Dieterich, and T. Brandt. 2003. “Eye Closure in Darkness Animates Sensory Systems.” *NeuroImage* 19 (3): 924–34. https://doi.org/10.1016/S1053-8119(03)00150-2.

Marzi, C., G. Tassinari, S. Aglioti, and L. Lutzemberger. 1986. “Spatial Summation across the Vertical Meridian in Hemianopics: A Test of Blindsight.” *Neuropsychologia* 24 (6): 749–758.

Mathewson, K., G. Gratton, M. Fabiani, D. Beck, and T. Ro. 2009. “To See or Not to See: Prestimulus α Phase Predicts Visual Awareness.” *Journal of Neuroscience* 29 (9): 2725–32. https://doi.org/10.1523/JNEUROSCI.3963-08.2009.

Mathewson, K., C. Prudhomme, M. Fabiani, D. Beck, A. Lleras, and G. Gratton. 2012. “Making Waves in the Stream of Consciousness: Entraining Oscillations in EEG Alpha and Fluctuations in Visual Awareness with Rhythmic Visual Stimulation.” *Journal of Cognitive Neuroscience* 24 (12): 2321–33. https://doi.org/10.1162/jocn_a_00288.

Mattingley, J., N. Berberovic, L. Corben, M. Slavin, M. Nicholls, and J. Bradshaw. 2004. “The Greyscales Task: A Perceptual Measure of Attentional Bias Following Unilateral Hemispheric Damage.” *Neuropsychologia* 42 (3): 387–394.

Mattingley, J., J. Bradshaw, J. Bradshaw, and N. Nettleton. 1994a. “Residual Rightward Attentional Bias after Apparent Recovery from Right Hemisphere Damage: Implications for a Multicomponent Model of Neglect.” *Journal of Neurology, Neurosurgery & Psychiatry* 57 (5): 597–604.

Mattingley, J., J. Bradshaw, N. Nettleton, and J. Bradshaw. 1994b. “Can Task Specific Perceptual Bias Be Distinguished from Unilateral Neglect?” *Neuropsychologia* 32 (7): 805–817.

McCourt, M. and M. Garlinghouse. 2000. “Asymmetries of Visuospatial Attention Are Modulated by Viewing Distance and Visual Field Elevation: Pseudoneglect in Peripersonal and Extrapersonal Space.” *Cortex* 36 (5): 715–31. https://doi.org/10.1016/S0010-9452(08)70548-3.

McCourt, M. and G. Jewell. 1999. “Visuospatial Attention in Line Bisection: Stimulusmodulation of Pseudoneglect.” *Neuropsychologia* 37 (7): 843–55. https://doi.org/10.1016/S0028-3932(98)00140-7.

McCourt, M., and C. Olafson. 1997. “Cognitive and Perceptual Influences on Visual Line Bisection: Psychophysical and Chronometric Analyses of Pseudoneglect.” *Neuropsychologia* 35 (3): 369–80. https://doi.org/10.1016/S0028-3932(96)00143-1.

McFadzean, R., D. Brosnahan, D. Hadley, and E. Mutlukan. 1994. “Representation of the Visual Field in the Occipital Striate Cortex.” *The British Journal of Ophthalmology* 78 (3): 185–90. https://doi.org/10.1136/bjo.78.3.185.

Milner, A. and R. McIntosh. 2005. “The Neurological Basis of Visual Neglect.” *Current Opinion in Neurology* 18 (6): 748. https://doi.org/10.1097/01.wco.0000191512.60368.ee.

Mishkin, M., L. Ungerleider, and K. Macko. 1983. “Object Vision and Spatial Vision: Two Cortical Pathways.” *Trends in Neurosciences* 6 (January): 414–17. https://doi.org/10.1016/0166-2236(83)90190-X.

Mitra, A., M. Abegg, J. Viswanathan, and J. Barton. 2010. “Line Bisection in Simulated Homonymous Hemianopia.” *Neuropsychologia* 48 (6): 1742–1749.

Montez, T., S. Poil, B. Jones, I. Manshanden, J. Verbunt, B. van Dijk, and A. Brussaard. 2009. “Altered Temporal Correlations in Parietal Alpha and Prefrontal Theta Oscillations in Early-Stage Alzheimer Disease.” *Proceedings of the National Academy of Sciences* 106 (5): 1614–19. https://doi.org/10.1073/pnas.0811699106.

Morland, A., J. Ogilvie, K. Ruddock, and J. Wright. 1996. “Orientation Discrimination Is Impaired in the Absence of the Striate Cortical Contribution to Human Vision.” *Proceedings of the Royal Society of London. Series B: Biological Sciences* 263 (1370): 633–640.

Munoz, D. and R. Wurtz. 1995a. “Saccade-Related Activity in Monkey Superior Colliculus. I. Characteristics of Burst and Buildup Cells.” *Journal of Neurophysiology* 73 (6): 2313–33. https://doi.org/10.1152/jn.1995.73.6.2313.

Munoz, D. and R. Wurtz. 1995b. “Saccade-Related Activity in Monkey Superior Colliculus. II. Spread of Activity during Saccades.” *Journal of Neurophysiology* 73 (6): 2334–48. https://doi.org/10.1152/jn.1995.73.6.2334.

Nicholls, M., J. Bradshaw, and J. Mattingley. 1999. “Free-Viewing Perceptual Asymmetries for the Judgement of Brightness, Numerosity and Size.” *Neuropsychologia* 37 (3): 307–14. https://doi.org/10.1016/S0028-3932(98)00074-8.

Niedermeyer, E. 1997. “Alpha Rhythms as Physiological and Abnormal Phenomena.” *International Journal of Psychophysiology* 26 (1): 31–49. https://doi.org/10.1016/S0167-8760(97)00754-X.

Nielsen, K., J. Intriligator, and J. Barton. 1999. “Spatial Representation in the Normal Visual Field: A Study of Hemifield Line Bisection.” *Neuropsychologia* 37 (3): 267–277.

Nobre, A., G. Sebestyen, D. Gitelman, M. Mesulam, R. Frackowiak, and C. Frith. 1997. “Functional Localization of the System for Visuospatial Attention Using Positron Emission Tomography.” *Brain* 120 (3): 515–33. https://doi.org/10.1093/brain/120.3.515.

Norton, J., S. Umunna, and T. Bretl. 2017. “The Elicitation of Steady-State Visual Evoked Potentials during Sleep.” *Psychophysiology* 54 (4): 496–507. https://doi.org/10.1111/psyp.12807.

Nowak, L. and J. Bullier. 1997. “The Timing of Information Transfer in the Visual System.” In *Extrastriate Cortex in Primates*, 205–241. Springer.

O’Neill, E., P. Connell, J. O’Connor, J. Brady, I. Reid, and P. Logan. 2011. “Prism Therapy and Visual Rehabilitation in Homonymous Visual Field Loss.” *Optometry and Vision Science: Official Publication of the American Academy of Optometry* 88 (2): 263–68. https://doi.org/10.1097/OPX.0b013e318205a3b8.

Onofrj, M., I. Bodis-Wollner, and L. Mylin. 1982. “Visual Evoked Potential Diagnosis of Field Defects in Patients with Chiasmatic and Retrochiasmatic Lesions.” *Journal of Neurology, Neurosurgery & Psychiatry* 45 (4): 294–302. https://doi.org/10.1136/jnnp.45.4.294.

Oostenveld, R., P. Fries, E. Maris, and J. Schoffelen. 2011. “FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data.” *Intell. Neuroscience* 2011 (January): 1:1–1:9. https://doi.org/10.1155/2011/156869.

Osterberg, G. 1935. “Topography of the Layer of the Rods and Cones in the Human Retima.” *Acta Ophthalmol* 13 (6): 1–102.

Palva, S., and J. Palva. 2007. “New Vistas for α-Frequency Band Oscillations.” *Trends in Neurosciences* 30 (4): 150–58. https://doi.org/10.1016/j.tins.2007.02.001.

Papageorgiou, E., G. Hardiess, F. Schaeffel, H. Wiethoelter, H. Karnath, H. Mallot, B. Schoenfisch, and U. Schiefer. 2007. “Assessment of Vision-Related Quality of Life in Patients with Homonymous Visual Field Defects.” *Graefe’s Archive for Clinical and Experimental Ophthalmology* 245 (12): 1749–58. https://doi.org/10.1007/s00417-007-0644-z.

Passamonti, C., C. Bertini, and E. Làdavas. 2009. “Audio-Visual Stimulation Improves Oculomotor Patterns in Patients with Hemianopia.” *Neuropsychologia* 47 (2): 546–555.

Pegna, A., A. Khateb, F. Lazeyras, and M. Seghier. 2005. “Discriminating Emotional Faces without Primary Visual Cortices Involves the Right Amygdala.” *Nature Neuroscience* 8 (1): 24–25. https://doi.org/10.1038/nn1364.

Perenin, M., and M. Jeannerod. 1975. “Residual Vision in Cortically Blind Hemiphields.” *Neuropsychologia* 13 (1): 1–7.

Perenin, M., and Y. Rossetti. 1996. “Grasping without Form Discrimination in a Hemianopic Field.” *Neuroreport: An International Journal for the Rapid Communication of Research in Neuroscience*.

Petersen, S., D. Robinson, and J. Morris. 1987. “Contributions of the Pulvinar to Visual Spatial Attention.” *Neuropsychologia* 25 (1): 97–105.

Pfurtscheller, G. 2001. “Functional Brain Imaging Based on ERD/ERS.” *Vision Research* 41 (10): 1257–60. https://doi.org/10.1016/S0042-6989(00)00235-2.

Pfurtscheller, G., C. Neuper, and W. Mohl. 1994. “Event-Related Desynchronization (ERD) during Visual Processing.” *International Journal of Psychophysiology* 16 (2): 147–53. https://doi.org/10.1016/0167-8760(89)90041-X.

Pietrelli, M., M. Zanon, E. Làdavas, P. Grasso, V. Romei, and C. Bertini. 2019. “Posterior Brain Lesions Selectively Alter Alpha Oscillatory Activity and Predict Visual Performance in Hemianopic Patients.” *Cortex*. https://doi.org/10.1016/j.cortex.2019.09.008.

Polyak, S. 1941. “The Retina.”

Pöppel, E. 1986. “Long-Range Colour-Generating Interactions across the Retina.” *Nature* 320 (6062): 523.

Pöppel, E., R. Held, and D. Frost. 1973. “Residual Visual Function after Brain Wounds Involving the Central Visual Pathways in Man.” *Nature* 243 (5405): 295–96. https://doi.org/10.1038/243295a0.

Prasad, S., and S. Galetta. 2011. “Anatomy and Physiology of the Afferent Visual System.” In *Handbook of Clinical Neurology*, 102:3–19. Elsevier.

Rabiller, G., J. He, Y. Nishijima, A. Wong, and J. Liu. 2015. “Perturbation of Brain Oscillations after Ischemic Stroke: A Potential Biomarker for Post-Stroke Function and Therapy.” *International Journal of Molecular Sciences* 16 (10): 25605–40. https://doi.org/10.3390/ijms161025605.

Rafal, R., J. Smith, J. Krantz, A. Cohen, and C. Brennan. 1990. “Extrageniculate Vision in Hemianopic Humans: Saccade Inhibition by Signals in the Blind Field.” *Science* 250 (4977): 118–121.

Rafal, R., K. Koller, J. Bultitude, P. Mullins, R. Ward, A. Mitchell, and A. Bell. 2015. “Connectivity between the Superior Colliculus and the Amygdala in Humans and Macaque Monkeys: Virtual Dissection with Probabilistic DTI Tractography.” *Journal of Neurophysiology* 114 (3): 1947–62. https://doi.org/10.1152/jn.01016.2014.

Rafal, R., and M. Posner. 1987. “Deficits in Human Visual Spatial Attention Following Thalamic Lesions.” *Proceedings of the National Academy of Sciences* 84 (20): 7349–7353.

Reddi, B., and R. Carpenter. 2000. “The Influence of Urgency on Decision Time.” *Nature Neuroscience* 3 (8): 827–30. https://doi.org/10.1038/77739.

Reynolds, J., T. Pasternak, and R. Desimone. 2000. “Attention Increases Sensitivity of V4 Neurons.” *Neuron* 26 (3): 703–714.

Riddoch, M., and G. Humphreys. 1983. “The Effect of Cueing on Unilateral Neglect.” *Neuropsychologia* 21 (6): 589–99. https://doi.org/10.1016/0028-3932(83)90056-8.

Rihs, T., C. Michel, and G. Thut. 2009. “A Bias for Posterior α-Band Power Suppression versus Enhancement during Shifting versus Maintenance of Spatial Attention.” *NeuroImage* 44 (1): 190–99. https://doi.org/10.1016/j.neuroimage.2008.08.022.

Robertson, I. 2001. “Do We Need the ‘Lateral’ in Unilateral Neglect? Spatially Nonselective Attention Deficits in Unilateral Neglect and Their Implications for

Rehabilitation." *NeuroImage* 14 (1): S85–90. https://doi.org/10.1006/nimg.2001.0838.

Rodman, H., C. Gross, and T. Albright. 1989. "Afferent Basis of Visual Response Properties in Area MT of the Macaque. I. Effects of Striate Cortex Removal." *Journal of Neuroscience* 9 (6): 2033–50. https://doi.org/10.1523/JNEUROSCI.09-06-02033.1989.

Rodman, H., C. Gross, and T. Albright. 1990. "Afferent Basis of Visual Response Properties in Area MT of the Macaque. II. Effects of Superior Colliculus Removal." *Journal of Neuroscience* 10 (4): 1154–64. https://doi.org/10.1523/JNEUROSCI.10-04-01154.1990.

Romei, V., V. Brodbeck, C. Michel, A. Amedi, A. Pascual-Leone, and G. Thut. 2008a. "Spontaneous Fluctuations in Posterior α-Band EEG Activity Reflect Variability in Excitability of Human Visual Areas." *Cerebral Cortex* 18 (9): 2010–18. https://doi.org/10.1093/cercor/bhm229.

Romei, V., J. Gross, and G. Thut. 2010. "On the Role of Prestimulus Alpha Rhythms over Occipito-Parietal Areas in Visual Input Regulation: Correlation or Causation?" *Journal of Neuroscience* 30 (25): 8692–97. https://doi.org/10.1523/JNEUROSCI.0160-10.2010.

Romei, V., T. Rihs, V. Brodbeck, and G. Thut. 2008b. "Resting Electroencephalogram Alpha-Power over Posterior Sites Indexes Baseline Visual Cortex Excitability." *NeuroReport* 19 (2): 203. https://doi.org/10.1097/WNR.0b013e3282f454c4.

Rorden, C., and M. Brett. 2000. "Stereotaxic Display of Brain Lesions." *Behavioural Neurology* 12 (4): 191–200.

Rorden, C., H. Karnath, and L. Bonilha. 2007. "Improving Lesion-Symptom Mapping." *Journal of Cognitive Neuroscience* 19 (7): 1081–88. https://doi.org/10.1162/jocn.2007.19.7.1081.

Rosanova, M., A. Casali, V. Bellina, F. Resta, M. Mariotti, and M. Massimini. 2009. "Natural Frequencies of Human Corticothalamic Circuits" 29 (24): 7679–85. https://doi.org/10.1523/JNEUROSCI.0445-09.2009.

Rossini, P., S. Rossi, C. Babiloni, and J. Polich. 2007. “Clinical Neurophysiology of Aging Brain: From Normal Aging to Neurodegeneration.” *Progress in Neurobiology* 83 (6): 375–400. https://doi.org/10.1016/j.pneurobio.2007.07.010.

Sadaghiani, S., and A. Kleinschmidt. 2016. “Brain Networks and α-Oscillations: Structural and Functional Foundations of Cognitive Control.” *Trends in Cognitive Sciences* 20 (11): 805–17. https://doi.org/10.1016/j.tics.2016.09.004.

Samaha, J., L. Iemi, and B. Postle. 2017. “Prestimulus Alpha-Band Power Biases Visual Discrimination Confidence, but Not Accuracy.” *Consciousness and Cognition*, Time course of event-related potentials associated with conscious experience, 54 (September): 47–55. https://doi.org/10.1016/j.concog.2017.02.005.

Samaha, J., and B. Postle. 2015. “The Speed of Alpha-Band Oscillations Predicts the Temporal Resolution of Visual Perception.” *Current Biology* 25 (22): 2985–90. https://doi.org/10.1016/j.cub.2015.10.007.

Sanchez-Lopez, J., C. Pedersini, F. Di Russo, N. Cardobi, C. Fonte, V. Varalta, M. Prior, N. Smania, S. Savazzi, and C. Marzi. 2019. “Visually Evoked Responses from the Blind Field of Hemianopic Patients.” *Neuropsychologia*, Neural Routes to Awareness in Vision, Emotion and Action: A tribute to Larry Weiskrantz, 128 (May): 127–39. https://doi.org/10.1016/j.neuropsychologia.2017.10.008.

Sarnthein, J., A. Morel, A. von Stein, and D. Jeanmonod. 2005. “Thalamocortical Theta Coherence in Neurological Patients at Rest and during a Working Memory Task.” *International Journal of Psychophysiology*, EEG Coherence, 57 (2): 87–96. https://doi.org/10.1016/j.ijpsycho.2005.03.015.

Schmolesky, M., Y. Wang, D. Hanes, K. Thompson, S. Leutgeb, J. Schall, and A. Leventhal. 1998. “Signal Timing across the Macaque Visual System.” *Journal of Neurophysiology* 79 (6): 3272–3278.

Schotten, M. de, F. Dell’Acqua, S. Forkel, A. Simmons, F. Vergani, D. Murphy, and M. Catani. 2011. “A Lateralized Brain Network for Visuospatial Attention.” *Nature Neuroscience* 14 (10): 1245–46. https://doi.org/10.1038/nn.2905.

Schuett, S., R. Dauner, and J. Zihl. 2011. “Line Bisection in Unilateral Homonymous Visual Field Defects.” *Cortex* 47 (1): 47–52.

Schurger, A., A. Cowey, and C. Tallon-Baudry. 2006. “Induced Gamma-Band Oscillations Correlate with Awareness in Hemianopic Patient GY.” *Neuropsychologia* 44 (10): 1796–1803. https://doi.org/10.1016/j.neuropsychologia.2006.03.015.

Sharon, O., and Y. Nir. 2018. “Attenuated Fast Steady-State Visual Evoked Potentials During Human Sleep.” *Cerebral Cortex* 28 (4): 1297–1311. https://doi.org/10.1093/cercor/bhx043.

Shipp, S., and S. Zeki. 1985. “Segregation of Pathways Leading from Area V2 to Areas V4 and V5 of Macaque Monkey Visual Cortex.” *Nature* 315 (6017): 322.

Sincich, L., and J. Horton. 2002. “Divided by Cytochrome Oxidase: A Map of the Projections from V1 to V2 in Macaques.” *Science* 295 (5560): 1734–1737.

Solcà, M., A. Guggisberg, A. Schnider, and B. Leemann. 2015. “Facial Blindsight.” *Frontiers in Human Neuroscience* 9: 522. https://doi.org/10.3389/fnhum.2015.00522.

Sommer, M., and R. Wurtz. 2004a. “What the Brain Stem Tells the Frontal Cortex. I. Oculomotor Signals Sent from Superior Colliculus to Frontal Eye Field via Mediodorsal Thalamus.” *Journal of Neurophysiology* 91 (3): 1381–1402.

Sommer, M., and R. Wurtz. 2004b. “What the Brain Stem Tells the Frontal Cortex. II. Role of the SC-MD-FEF Pathway in Corollary Discharge.” *Journal of Neurophysiology* 91 (3): 1403–1423.

Spering, M., and M. Carrasco. 2015. “Acting without Seeing: Eye Movements Reveal Visual Processing without Awareness.” *Trends in Neurosciences* 38 (4): 247–258.

Spjøtvoll, E., and M. Stoline. 1973. “An Extension of the T-Method of Multiple Comparison to Include the Cases with Unequal Sample Sizes.” *Journal of the American Statistical Association* 68 (344): 975–78. https://doi.org/10.1080/01621459.1973.10481458.

Sponheim, S., B. Clementz, W. Iacono, and M. Beiser. 2000. “Clinical and Biological Concomitants of Resting State EEG Power Abnormalities in Schizophrenia.” *Biological Psychiatry* 48 (11): 1088–97. https://doi.org/10.1016/S0006-3223(00)00907-0.

Stam, C., A. Hillebrand, H. Wang, and P. Mieghem. 2010. “Emergence of Modular Structure in a Large-Scale Brain Network with Interactions between Dynamics and

Connectivity." *Frontiers in Computational Neuroscience* 4. https://doi.org/10.3389/fncom.2010.00133.

Stein, A., and J. Sarnthein. 2000. "Different Frequencies for Different Scales of Cortical Integration: From Local Gamma to Long Range Alpha/Theta Synchronization." *International Journal of Psychophysiology* 38 (3): 301–13. https://doi.org/10.1016/S0167-8760(00)00172-0.

Stoerig, P., and E. Pöppel. 1986. "Eccentricity-Dependent Residual Target Detection in Visual Field Defects." *Experimental Brain Research* 64 (3): 469–475.

Stoerig, P. 1987. "Chromaticity and Achromaticity: Evidence for a Functional Differentiation in Visual Field Defects." *Brain* 110 (4): 869–886.

Stoerig, P., and A. Cowey. 1989. "Wavelength Sensitivity in Blindsight." *Nature* 342 (6252): 916.

Stoerig, P., and A. Cowey. 1991. "Increment-Threshold Spectral Sensitivity in Blindsight: Evidence for Colour Opponency." *Brain* 114 (3): 1487–1512.

Stoerig, P., M. Hübner, and E. Pöppel. 1985. "Signal Detection Analysis of Residual Vision in a Field Defect Due to a Post-Geniculate Lesion." *Neuropsychologia* 23 (5): 589–599.

Stoerig, P., and Fahle, M. 1995. "Apparent motion across a scotoma: an implicit test of blindsight". E*ur J Neurosci Suppl*, 8, 76.

Striemer, C., R. Whitwell, and M. Goodale. 2019. "Affective Blindsight in the Absence of Input from Face Processing Regions in Occipital-Temporal Cortex." *Neuropsychologia* 128: 50–57. https://doi.org/10.1016/j.neuropsychologia.2017.11.014.

Tamietto, M., F. Cauda, L. Corazzini, S. Savazzi, C. Marzi, R. Goebel, L. Weiskrantz, and B. de Gelder. 2010. "Collicular Vision Guides Nonconscious Behavior." *Journal of Cognitive Neuroscience* 22 (5): 888–902.

Tamietto, M., and M. Morrone. 2016. "Visual Plasticity: Blindsight Bridges Anatomy and Function in the Visual System." *Current Biology* 26 (2): R70–R73.

Tamietto, M., P. Pullens, B. de Gelder, L. Weiskrantz, and R. Goebel. 2012. "Subcortical Connections to Human Amygdala and Changes Following Destruction of the Visual Cortex." *Current Biology* 22 (15): 1449–1455.

Tant, M., W. Brouwer, F. Cornelissen, and A. Kooijman. 2002a. “Driving and Visuospatial Performance in People with Hemianopia.” *Neuropsychological Rehabilitation* 12 (5): 419–437.

Tant, M., F. Cornelissen, A. Kooijman, and W. Brouwer. 2002b. “Hemianopic Visual Field Defects Elicit Hemianopic Scanning.” *Vision Research* 42 (10): 1339–1348.

Tecchio, F., F. Zappasodi, P. Pasqualetti, M. Tombini, C. Salustri, A. Oliviero, V. Pizzella, F. Vernieri, and P. Rossini. 2005. “Rhythmic Brain Activity at Rest from Rolandic Areas in Acute Mono-Hemispheric Stroke: A Magnetoencephalographic Study.” *NeuroImage* 28 (1): 72–83. https://doi.org/10.1016/j.neuroimage.2005.05.051.

Thut, G., A. Nietzel, S. Brandt, and A. Pascual-Leone. 2006. “α-Band Electroencephalographic Activity over Occipital Cortex Indexes Visuospatial Attention Bias and Predicts Visual Target Detection.” *Journal of Neuroscience* 26 (37): 9494–9502. https://doi.org/10.1523/JNEUROSCI.0875-06.2006.

Thut, G., D. Veniero, V. Romei, C. Miniussi, P. Schyns, and J. Gross. 2011. “Rhythmic TMS Causes Local Entrainment of Natural Oscillatory Signatures.” *Current Biology* 21 (14): 1176–85. https://doi.org/10.1016/j.cub.2011.05.049.

Tipura, E., A. Pegna, B. de Gelder, and O. Renaud. 2017. “Visual Stimuli Modulate Frontal Oscillatory Rhythms in a Cortically Blind Patient: Evidence for Top-down Visual Processing.” *Clinical Neurophysiology* 128 (5): 770–79. https://doi.org/10.1016/j.clinph.2017.02.009.

Tononi, G., and G. Edelman. 1998. “Consciousness and Complexity.” *Science* 282 (5395): 1846–51. https://doi.org/10.1126/science.282.5395.1846.

Tootell, R., S. Hamilton, M. Silverman, and E. Switkes. 1988. “Functional Anatomy of Macaque Striate Cortex. I. Ocular Dominance, Binocular Interactions, and Baseline Conditions.” *Journal of Neuroscience* 8 (5): 1500–1530.

Tootell, R., J. Reppas, K. Kwong, R. Malach, R. Born, T. Brady, B. Rosen, and J. Belliveau. 1995. “Functional Analysis of Human MT and Related Visual Cortical Areas Using Magnetic Resonance Imaging.” *Journal of Neuroscience* 15 (4): 3215–3230.

Tran, A., M. MacLean, V. Hadid, L. Lazzouni, D. Nguyen, J. Tremblay, M. Dehaes, and F. Lepore. 2019. “Neuronal Mechanisms of Motion Detection Underlying Blindsight Assessed by Functional Magnetic Resonance Imaging (FMRI).” *Neuropsychologia*,

Neural Routes to Awareness in Vision, Emotion and Action: A tribute to Larry Weiskrantz, 128 (May): 187–97. https://doi.org/10.1016/j.neuropsychologia.2019.02.012.

Travis, F., and R. Wallace. 1999. “Autonomic and EEG Patterns during Eyes-Closed Rest and Transcendental Meditation (TM) Practice: The Basis for a Neural Model of TM Practice.” *Consciousness and Cognition* 8 (3): 302–18. https://doi.org/10.1006/ccog.1999.0403.

Treue, S., and J. Maunsell. 1996. “Attentional Modulation of Visual Motion Processing in Cortical Areas MT and MST.” *Nature* 382 (6591): 539.

Twemlow, S., and W. Bowen. 1977. “Sociocultural Predictors of Self-Actualization in EEG-Biofeedback-Treated Alcoholics.” *Psychological Reports* 40 (2): 591–98. https://doi.org/10.2466/pr0.1977.40.2.591.

Valera, F., A. Toro, E. John, and E. Schwartz. 1981. “Perceptual Framing and Cortical Alpha Rhythm.” *Neuropsychologia* 19 (5): 675–86. https://doi.org/10.1016/0028-3932(81)90005-1.

Van Buren, J., and M. Baldwin. 1958. “The Architecture of the Optic Radiation in the Temporal Lobe of Man.” *Brain* 81 (1): 15–40.

Van den Stock, J., M. Tamietto, B. Sorger, S. Pichon, J. Grézes, and B. de Gelder. 2011. “Cortico-Subcortical Visual, Somatosensory, and Motor Activations for Perceiving Dynamic Whole-Body Emotional Expressions with and without Striate Cortex (V1).” *Proceedings of the National Academy of Sciences* 108 (39): 16188–16193.

Van den Stock, J., M. Tamietto, M. Zhan, A. Heinecke, A. Hervais-Adelman, L. Legrand, A. Pegna, and B. de Gelder. 2014. “Neural Correlates of Body and Face Perception Following Bilateral Destruction of the Primary Visual Cortices.” *Frontiers in Behavioral Neuroscience* 8. https://doi.org/10.3389/fnbeh.2014.00030.

Van der Stigchel, S., W. Zoest, J. Theeuwes, and J. Barton. 2008. “The Influence of ‘Blind’ Distractors on Eye Movement Trajectories in Visual Hemifield Defects.” *Journal of Cognitive Neuroscience* 20 (11): 2025–2036.

Van Horn, S., A. Erişir, and S. Sherman. 2000. “Relative Distribution of Synapses in the A-Laminae of the Lateral Geniculate Nucleus of the Cat.” *Journal of Comparative Neurology* 416 (4): 509–520.

Varela, F., J. Lachaux, E. Rodriguez, and J. Martinerie. 2001. “The Brainweb: Phase Synchronization and Large-Scale Integration.” *Nature Reviews Neuroscience* 2 (4): 229–39. https://doi.org/10.1038/35067550.

Vialatte, F., M. Maurice, J. Dauwels, and A. Cichocki. 2010. “Steady-State Visually Evoked Potentials: Focus on Essential Paradigms and Future Perspectives.” *Progress in Neurobiology* 90 (4): 418–38. https://doi.org/10.1016/j.pneurobio.2009.11.005.

Vinck, M., R. Oostenveld, M. van Wingerden, F. Battaglia, and C. Pennartz. 2011. “An Improved Index of Phase-Synchronization for Electrophysiological Data in the Presence of Volume-Conduction, Noise and Sample-Size Bias.” *NeuroImage* 55 (4): 1548–65. https://doi.org/10.1016/j.neuroimage.2011.01.055.

Visser, G., G. Wieneke, A. VanHuffelen, J. DeVries, and P. Bakker. 2001. “The Development of Spectral EEG Changes During Short Periods of Circulatory Arrest.” *Journal of Clinical Neurophysiology* 18 (2): 169.

Volavka, J., M. Matoušek, and J. Roubíček. 1967. “Mental Arithmetic and Eye Opening. An EEG Frequency Analysis and GSR Study.” *Electroencephalography and Clinical Neurophysiology* 22 (2): 174–76. https://doi.org/10.1016/0013-4694(67)90158-7.

Walker, R., H. Deubel, W. Schneider, and J. Findlay. 1997. “Effect of Remote Distractors on Saccade Programming: Evidence for an Extended Fixation Zone.” *Journal of Neurophysiology* 78 (2): 1108–19. https://doi.org/10.1152/jn.1997.78.2.1108.

Walker, R., R. Kentridge, and J. Findlay. 1995. “Independent Contributions of the Orienting of Attention, Fixation Offset and Bilateral Stimulation on Human Saccadic Latencies.” *Experimental Brain Research* 103 (2): 294–310. https://doi.org/10.1007/bf00231716.

Walker, R., S. Mannan, D. Maurer, A. Pambakian, and C. Kennard. 2000. “The Oculomotor Distractor Effect in Normal and Hemianopic Vision.” *Proceedings. Biological Sciences* 267 (1442): 431–38. https://doi.org/10.1098/rspb.2000.1018.

Walker, R., and V. Benson. 2013. “Remote Distractor Effects and Saccadic Inhibition: Spatial and Temporal Modulation.” *Journal of Vision* 13 (11): 9–9. https://doi.org/10.1167/13.11.9.

Wan, L., H. Huang, N. Schwab, J. Tanner, A. Rajan, N. Lam, L. Zaborszky, C. Li, C. Price, and M. Ding. 2019. “From Eyes-Closed to Eyes-Open: Role of Cholinergic

Projections in EC-to-EO Alpha Reactivity Revealed by Combining EEG and MRI." *Human Brain Mapping* 40 (2): 566–77. https://doi.org/10.1002/hbm.24395.

Wang, L., X. Guo, J. Sun, Z. Jin, and S. Tong. 2012. "Cortical Networks of Hemianopia Stroke Patients: A Graph Theoretical Analysis of EEG Signals at Resting State." *Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference* 2012: 49–52. https://doi.org/10.1109/EMBC.2012.6345868.

Weiskrantz, L. 1990. *Blindsight: A Case Study and Implications*. Oxford University Press. https://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780198521921.001.0001/acprof-9780198521921.

Weiskrantz, L., E. Warrington, M. Sanders, and J. Marshall. 1974. "Visual Capacity in the Hemianopic Field Following a Restricted Occipital Ablation." *Brain* 97 (4): 709–728.

Westlake, K., L. Hinkley, M. Bucci, A. Guggisberg, A. Findlay, R. Henry, S. Nagarajan, and N. Byl. 2012. "Resting State Alpha-Band Functional Connectivity and Recovery after Stroke." *Experimental Neurology* 237 (1): 160–69. https://doi.org/10.1016/j.expneurol.2012.06.020.

Wilson, B., J. Cockburn, and P. Halligan. 1987. "Development of a Behavioral Test of Visuospatial Neglect." *Archives of Physical Medicine and Rehabilitation* 68 (2): 98–102.

Wu, W., J. Sun, Z. Jin, X. Guo, Y. Qiu, Y. Zhu, and S. Tong. 2011. "Impaired Neuronal Synchrony after Focal Ischemic Stroke in Elderly Patients." *Clinical Neurophysiology* 122 (1): 21–26. https://doi.org/10.1016/j.clinph.2010.06.003.

Wutz, A., D. Melcher, and J. Samaha. 2018. "Frequency Modulation of Neural Oscillations According to Visual Task Demands." *Proceedings of the National Academy of Sciences* 115 (6): 1346–51. https://doi.org/10.1073/pnas.1713318115.

Wutz, A., E. Muschter, M. van Koningsbruggen, N. Weisz, and D. Melcher. 2016. "Temporal Integration Windows in Neural Processing and Perception Aligned to Saccadic Eye Movements." *Current Biology* 26 (13): 1659–68. https://doi.org/10.1016/j.cub.2016.04.070.

Xu, P., X. Xiong, Q. Xue, Y. Tian, Y. Peng, R. Zhang, P. Li, Y. Wang, and D. Yao. 2014. "Recognizing Mild Cognitive Impairment Based on Network Connectivity Analysis of Resting EEG with Zero Reference." *Physiological Measurement* 35 (7): 1279–98. https://doi.org/10.1088/0967-3334/35/7/1279.

Zangemeister, W., and U. Oechsner. 1996. "Evidence for Scanpaths in Hemianopic Patients Shown through String Editing Methods." In *Advances in Psychology*, 116:197–221. Elsevier.

Zeki, S. 1980. "The Representation of Colours in the Cerebral Cortex." *Nature* 284 (5755): 412.

Zhang, X., S. Kedar, M. Lynn, N. Newman, and V. Biousse. 2006. "Homonymous Hemianopias: Clinical-Anatomic Correlations in 904 Cases." *Neurology* 66 (6): 906–10. https://doi.org/10.1212/01.wnl.0000203913.12088.93.

Zihl, J. 1995a. "Visual Scanning Behavior in Patients with Homonymous Hemianopia." *Neuropsychologia* 33 (3): 287–303. https://doi.org/10.1016/0028-3932(94)00119-a.

Zihl, J. 1995b. "Eye Movement Patterns in Hemianopic Dyslexia." *Brain: A Journal of Neurology* 118 (Pt 4) (August): 891–912. https://doi.org/10.1093/brain/118.4.891.

Zihl, J., and D. von Cramon. 1985. "Visual Field Recovery from Scotoma in Patients with Postgeniculate Damage. A Review of 55 Cases." *Brain: A Journal of Neurology* 108 (Pt 2) (June): 335–65. https://doi.org/10.1093/brain/108.2.335.

Zihl, J., P. Sämann, T. Schenk, S. Schuett, and R. Dauner. 2009. "On the Origin of Line Bisection Error in Hemianopia." *Neuropsychologia* 47 (12): 2417–2426.